

A Thesis Presented to
The Faculty of Alfred University

Reactions Mediated by the Conducting Polymer Poly-(3,4-ethylenedioxythiophene) (PEDOT)

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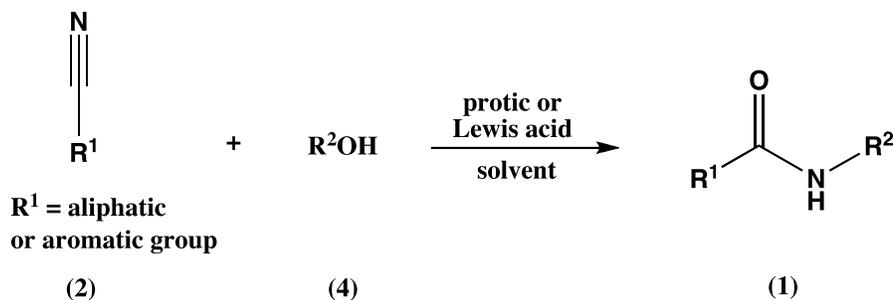
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INTRODUCTION

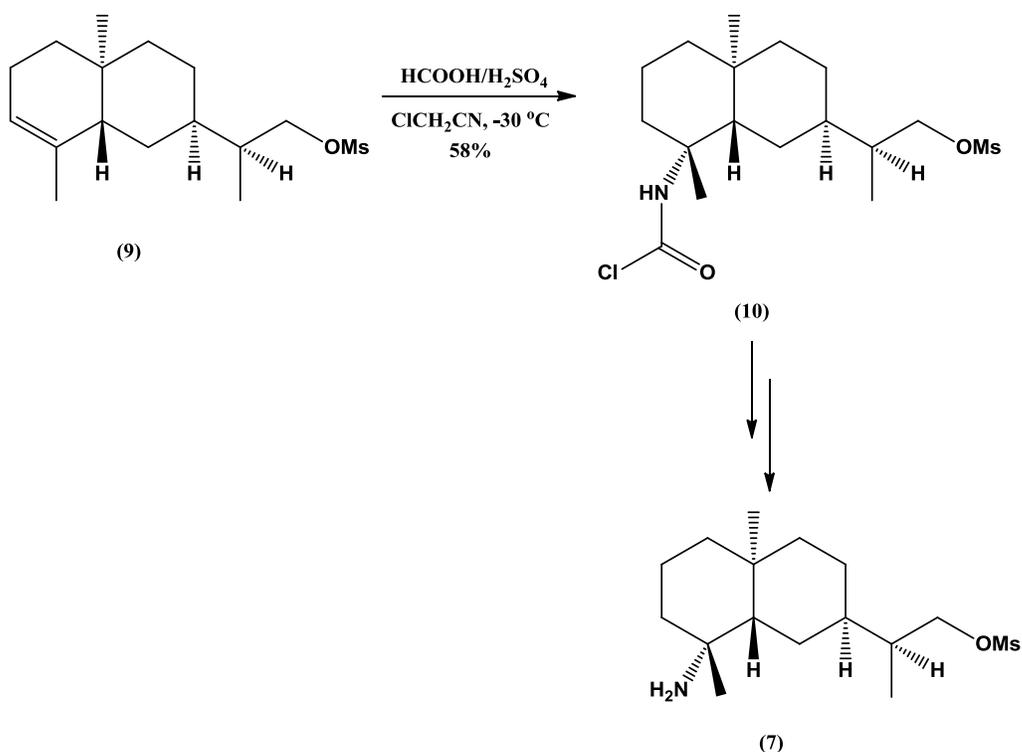
The Ritter Reaction:

The reaction involving formation of *n*-carboxamides (**1**) from aliphatic or aromatic nitriles (**2**) and carbocations (**3**) is known as the Ritter reaction and was first reported by J. J. Ritter and P. P. Minieri in 1948 (Scheme 1).¹



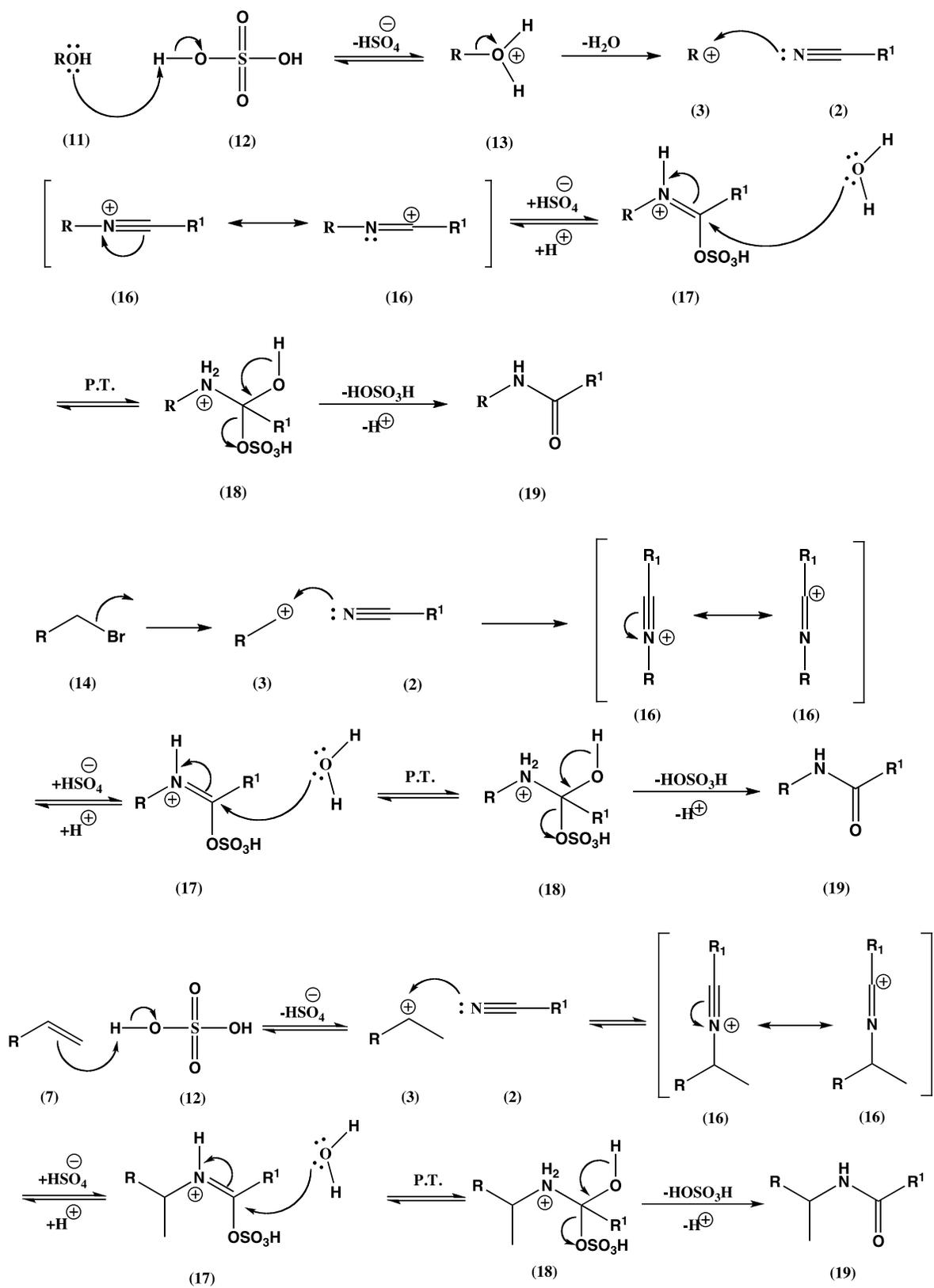
Scheme 1: General Ritter Reaction

The Ritter reaction has been widely used for the preparation of acyclic amides as well as heterocycles, including lactams (**4**), oxazolines (**5**), and dihydroisoquinolines (**6**).¹ In addition, the reaction has been used in the synthesis of certain natural product derivatives, such as in the completion of the first total synthesis of (-)-4-epiaxinyssamine (**7**), an epimer of axinyssamine (**8**), the latter of which shows cytotoxic activity against tumor cell lines. The Ritter reaction was used in this synthesis by way of treatment of a key olefinic intermediate (**9**) with chloroacetonitrile to furnish the chloroacetamide (**10**). A series of reactions followed to furnish the (-)-4-epiaxinyssamine (Scheme 2).²



Scheme 2: Ritter Reaction in the Synthesis of (-)-4-epiaxinyssamine

Because of its synthetic utility, the mechanism of the Ritter reaction has been widely studied. When tertiary-, secondary-, or benzylic alcohols (**11**), are treated with a strong protic (**12**) or Lewis acid, a carbocation is formed after the elimination of water (**13**). When the acid is used to treat alkyl halides (**14**), an S_N1 reaction occurs during which the carbocation is furnished, with alkenes (**15**), the carbocation is formed after protonation of the carbon-carbon double bond. A nitrile then attacks the cation and the intermediate nitrilium ion (**16**) is then attacked by the conjugate base of the mediating acid resulting in formation of an imidate (**17**). Subsequent hydration furnishes the hydrated intermediate (**18**), which rearranges to the desired amide (**19**). In cases where the reaction occurs intramolecularly, a lactam product is formed (Scheme 3).¹



Scheme 3: Mechanism of the Ritter Reaction

The use of the aforementioned strong protic or Lewis acids results in the exclusion from or protection of certain acid-sensitive functional groups on the substrate. Utilization of more selective reagents may result in the ability to use these acid-sensitive functional groups, thereby potentially eliminating protection steps.

Conducting Polymers:

General Uses

Conducting polymers are typically used for applications in gas sensors, pH sensors, pLEDs, electrolyte-gate transistors, and energy storage.³ A newer study has reported potential methods of overcoming challenges facing applications of conducting polymers in drug delivery, including bilayered conducting polymers, nanostructured conducting polymers, biotinylated conducting polymers, and conducting hydrogels.⁴ An additional study has shown the polymerization of PEDOT around living neural cells (Figure 1), which could be potentially beneficial in nerve repair. This was done safely as far as cell viability is concerned as the cells lived for at least 120 hours after polymerization.⁵

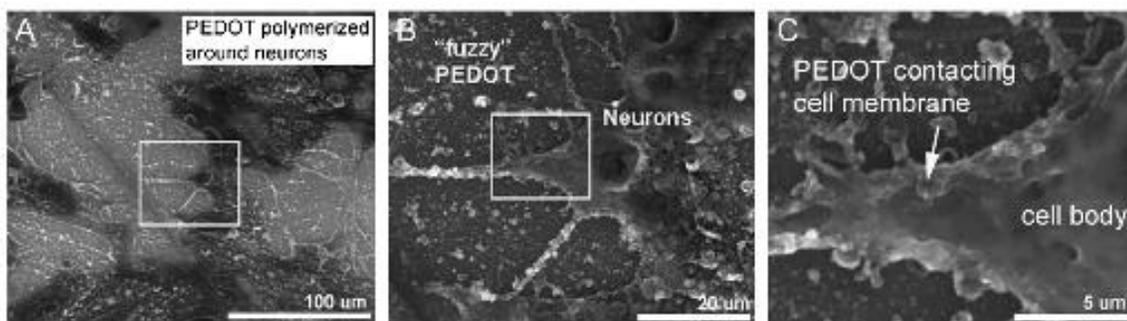
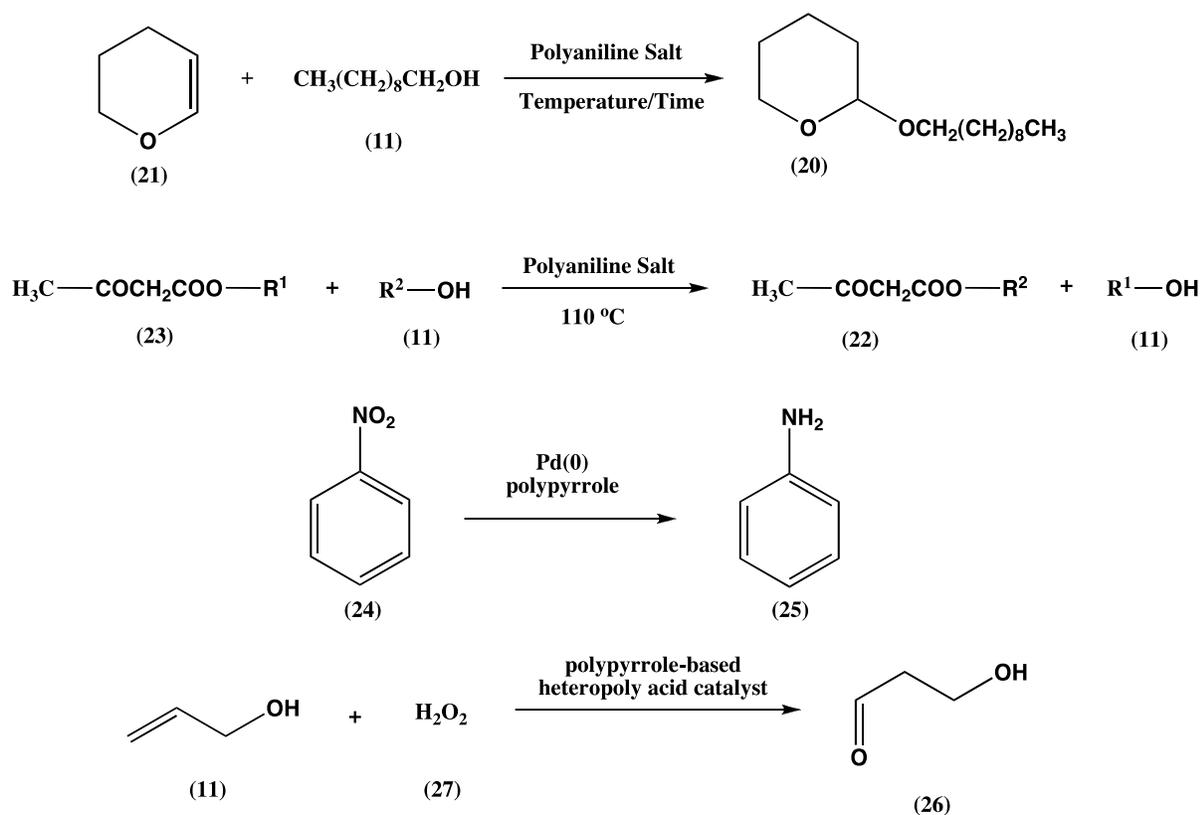


Figure 1: Polymerization of PEDOT around living neural cells

Reactions

Recently, it has been shown that certain polymer-bound acids can mediate reactions such as: polyaniline salts loaded with H_2SO_4 or HNO_3 to furnish tetrahydropyranylation products (**20**) from 3,4-dihydro-2H-pyran (**21**) and alcohols,⁶ polyaniline salts loaded with H_2SO_4 , HCl or HNO_3 to form transesterification products (**22**) from certain esters (**23**) and alcohols,⁷ polypyrrole with $\text{Pd}(0)$ or $\text{Pd}(\text{II})$ to hydrogenate nitrobenzene (**24**) to aniline (**25**),⁸ and polypyrrole-based heteropoly acid catalysts for eliminations and oxidations (**26**) on alcohols with hydrogen peroxide (**27**) (Scheme 4).⁹



Scheme 4: Reactions of Polymer-Bound Acids

Poly-(3,4-ethylenedioxythiophene) (PEDOT):

The accepted structure of the conducting polymer, poly-(3,4-ethylenedioxythiophene) (PEDOT) (Figure 2), used in our study is a repeating trimer with a triflate counter ion.¹⁰

PEDOT has been shown to mediate formation of homoethers (**28**) from alcohols with small amounts of oxidation to the corresponding ketone or aldehyde (**29**) (Scheme 9);¹¹ Friedel-Crafts alkylations (**30**) of benzene and toluene with alcohols (Scheme 10);¹² and cyclodehydrations (**31**) of acyclic sugars (**32**) (Scheme 11).¹³

The advantages of using PEDOT include that it is a heterogeneous catalyst, allowing for ease of product separation and reuse of the polymer.

The disadvantages of PEDOT include that it is very expensive at a current cost of approximately 220 dollars for a dispersion of the polymer in 25 milliliters of water. The production process of PEDOT involves running a current through a mixture of EDOT, the monomer of PEDOT, in acetonitrile before scraping the collected polymer off the anode. This process is tedious and is not particularly high yielding. Finally, PEDOT is very statically charged and is easily lost during transfer to the reaction flask meaning that the exact amount of PEDOT used in each reaction may be incorrect.

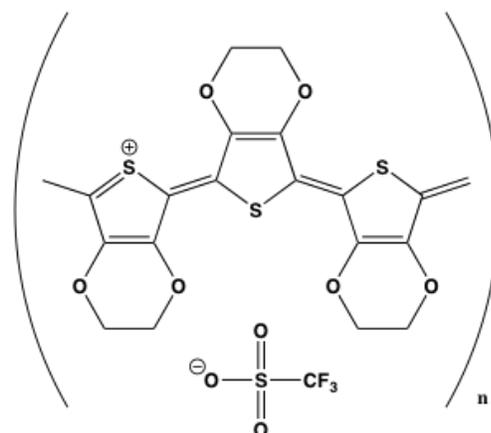
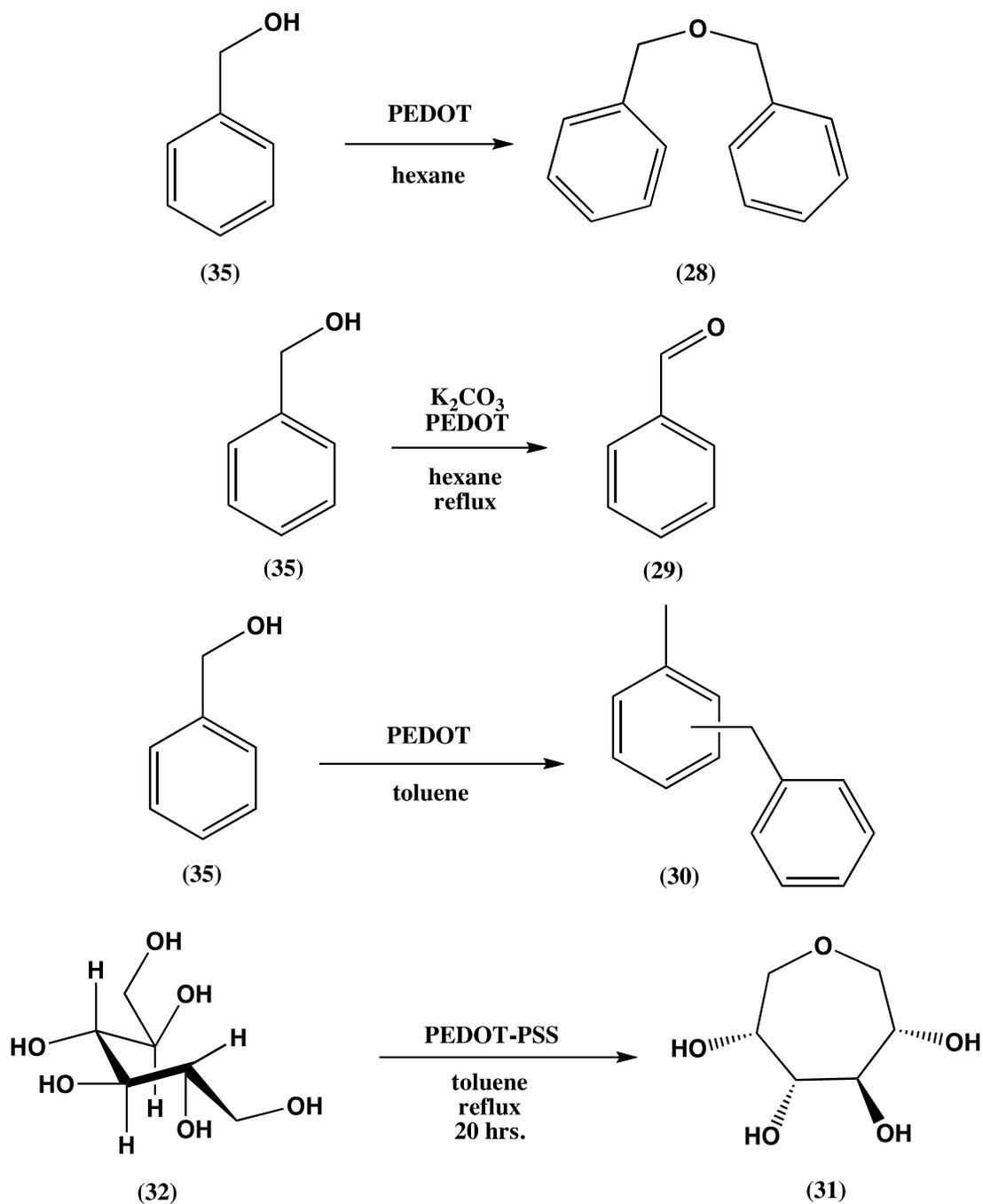


Figure 2: Poly-(3,4-ethylenedioxythiophene)



Scheme 11: PEDOT-Mediated Reactions

The Ritter Reaction and PEDOT:

Our studies have shown that PEDOT can mediate the Ritter reaction in place of the Lewis or protic acid to furnish the acetamide product. This, combined with the supposition

that triflic acid is not responsible for the progress of the reaction, suggests that PEDOT can mediate the Ritter reaction under mild conditions and it may now be possible to use unprotected, acid-sensitive functional groups.

In an attempt to determine the scope of the PEDOT-mediated Ritter reaction, a number of alcohols were reacted with acetonitrile. Given that these reactions used acetonitrile as both the solvent and substrate, a new solvent was required in order to perform these reactions with a stoichiometric ratio of alcohol and nitrile. In previous studies, it was found that PEDOT could mediate certain reactions in toluene. However, a Friedel-Crafts alkylation takes place between toluene and the carbocation, which is putatively generated from the interaction between the PEDOT and the alcohol, making it an undesirable solvent.¹⁴ After testing a number of solvents, nitromethane was identified as an acceptable solvent. In addition to probing the scope of the reaction with a variety of alcohols, nitrile versatility in the PEDOT-mediated Ritter reaction was also examined.

In an effort to minimize by-products, attempts to optimize the ratio of nitrile to alcohol have been made utilizing diphenylmethanol (**33**) and benzonitrile (**34**). The selection alcohol **33** and nitrile **34** as substrates was a result of diphenylmethanol having been the most successful alcohol in Ritter reactions mediated by PEDOT in acetonitrile and the belief that benzonitrile should be deactivated because of the electron-withdrawing nature of the benzene ring. Because of this, it should follow that any optimizations useful to benzonitrile would be useful to other nitriles. The results obtained using PEDOT were compared with sulfuric acid, a more traditional initiator of Ritter reactions (Table 2). While work on these stoichiometric reactions is ongoing, this was the first instance in which we were able to show that PEDOT can be used as a mediator in Ritter reactions of alcohols and nitriles in non-nitrile solvents.

From here, we were able to confidently pursue the previously mentioned reactions between benzyl alcohol (**35**) and diphenylmethanol with a variety of nitriles.

As previously mentioned, understanding the mechanism of PEDOT-mediated reactions is not only synthetically important, but may also lead to the production of novel polymer reagents at lower costs than PEDOT. The reactions of triphenylmethanol (**36**) and adamantanol (**37**) both suggest that the PEDOT is being approached directly by the alcohol. This finding was concluded from the difficulty associated with performing these reactions. With triphenylmethanol, PEDOT showed no reaction, but sulfuric acid and Amberlite, which function by way of an H^+ , both furnished high yields. The diphenylmethanol had a relatively good yield with PEDOT, but took approximately 32 hours to reach completion.

Our studies suggest that PEDOT behaves as an alcohol-selective Lewis acid, and that it is not the presence of a polymer-bound acid that is catalyzing the reaction. Given that the

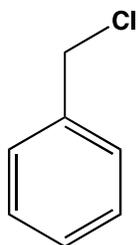


Figure 4: Benzyl chloride

Ritter reaction can take place between alcohols, alkenes, and halides, reactions utilizing styrene (Figure 3) and benzyl chloride (Figure 4) were done in refluxing acetonitrile.

Benzyl chloride would ordinarily react with other Lewis

acids and the fact that both it and styrene showed no

observable reaction via GCMS suggests that PEDOT is

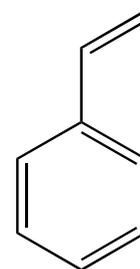


Figure 3: Styrene

an alcohol-selective, perhaps even specific, Lewis acid. Concerns arose that trace amounts of triflic acid, either already present or generated in situ, were responsible for reaction progress.

To test this, a reaction of naphthalenemethanol (**38**), 3,4-dihydro-2*H*-pyran, and PEDOT in benzene was performed as well as a similar reaction using Amberlite, a known polymer-bound acid, in the place of PEDOT. Not only did each reaction yield different sets of products, but PEDOT, unlike Amberlite, also appears to have reacted preferentially with the naphthalenemethanol rather than the pyran, which suggests that the PEDOT-mediated Ritter reaction would proceed under milder reaction conditions and that acid-sensitive functional groups, such as alkenes, could be present on the substrate. In the future, it may be even more beneficial to perform the same experiment using Amberlyst, another known polymer-bound acid, in the place of Amberlite. Both Amberlyst and triflic acid function by way of a sulfuric acid moiety, thus, they are more comparable than triflic acid and Amberlite, which functions by way of a carboxylic acid moiety. Finally, an exhaustion study was performed to ascertain whether or not PEDOT could be deactivated over the course of many reactions.¹⁵

In addition to the Ritter reaction, our studies show that PEDOT can mediate Friedel-Crafts alkylations and enol alkylations. It was previously shown that Friedel-Crafts alkylations could be mediated by PEDOT and was only proven with the aromatic substrate also acting as the solvent. However, our reaction was done in a non-aromatic solvent with stoichiometric amounts of the aromatic substrate. The results of these reactions are discussed herein.

RESULTS

PEDOT-Mediated Ritter Reactions with Various Alcohols:

In simultaneously exploring the scope of the PEDOT-mediated Ritter reactions and comparing their results to more traditional reagents, the alcohols in this study were separately treated with PEDOT, sulfuric acid, and Amberlyst 15 in acetonitrile at reflux (Scheme 11 and Table 1). Reactions of alcohols with sulfuric acid and Amberlyst generated the desired amide product in good yields in cases where the carbocation was sufficiently stabilized (Table 1, entries 1-4, 6 and 7). In every case, reactions mediated by sulfuric acid showed faster conversion rates than those mediated by Amberlyst as observed by GCMS. Given that cyclohexanol (**39**) was converted to the desired amide product in very low yields, with the major byproduct (observed by GCMS) being cyclohexene (Figure 5), it is reasonable to conclude that alcohols containing β -hydrogens suitable for elimination reactions will do so to the appropriate alkene. However, the byproducts are unable to be isolated due to low boiling points (Table 1, entries 5, 6, 8, and 9). In alcohols where this is not possible, the yields of our desired amide products increase significantly. Furthermore, in sulfuric acid-mediated reactions of primary alcohols including benzyl alcohol, isobutyl alcohol (**40**), and 1-butanol (**41**), the observed byproducts were benzyl acetate (**42**), isobutyl acetate (**43**), and butyl acetate (**44**), which resulted from the alcohol acting as a nucleophile by a 1,2-addition into the acetonitrile followed by subsequent hydrolysis of the imine (Figure 6).

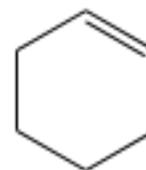


Figure 5:
Cyclohexene

Secondary and tertiary alcohols such as isopropyl alcohol (**45**), cyclohexanol, and *tert*-butanol (**46**) suffered poor reactivity with sulfuric acid and Amberlyst and no reactivity observable by the GCMS with PEDOT (Table 1, entries 5 and 10). These observations may

be the result of the difficulty of forming the carbocations associated with these alcohols; however, the GCMS temperature conditions were too high to observe any unreacted alcohols. Because of this, it was not possible to monitor disappearance of the alcohol in order to determine whether or not another reaction was taking place, such as an elimination reaction.

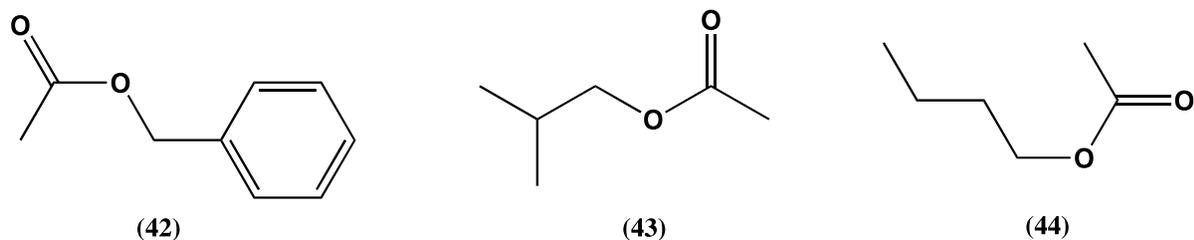


Figure 6: From left to right, benzyl acetate, isobutyl acetate, and butyl acetate

It is interesting to note the poor reactivity of benzyl alcohol compared to naphthalenemethanol with PEDOT. Where naphthalenemethanol is concerned, almost of all

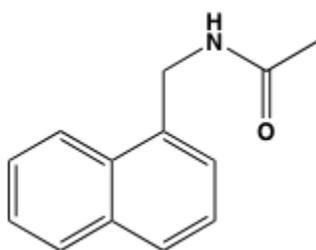


Figure 7: *N*-(naphthalen-1-ylmethyl)ethanamide

of the starting material was consumed and, after chromatographic purification, the desired *N*-(naphthalen-1-ylmethyl)ethanamide product (Figure 7) was furnished in 70% isolated yield. The relative reactivity of these alcohols with

PEDOT is consistent with previous reports where Friedel-

Crafts alkylations showed greater alcohol consumption with naphthalenemethanol than with benzyl alcohol in benzene at reflux. With toluene, which has a higher boiling point than benzene, greater consumption of the starting material was observed.¹⁵ The higher degree of resonance stabilization of the carbocation associated with naphthalenemethanol may account for increased conversion compared to benzyl alcohol.

Consistent with this premise, the reaction of diphenylmethanol was the most efficient

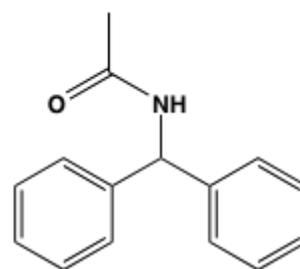
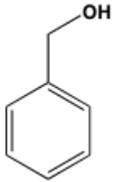
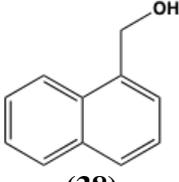
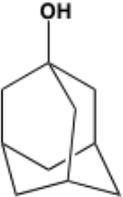
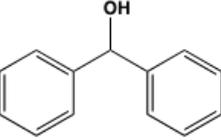
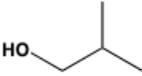
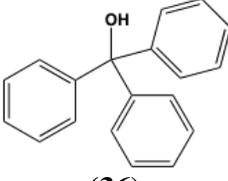
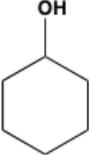


Figure 8: *N*-benzhydrylethanamide

PEDOT-mediated reaction. All of the alcohol was consumed as seen by the GCMS after only 3 hours reaction time. The desired *N*-benzhydrylethanamide product (Figure 8) was isolated after chromatographic purification in 91% yield.¹⁶

Table 1: Results summarizing H₂SO₄, Amberlite, and PEDOT-mediated Ritter reactions with alcohols in acetonitrile

Entry #	Alcohol	Initiator	Isolated Yield (%)	Alcohol	Initiator	Isolated Yield (%)
1,6	 (35)	PEDOT	<1	 (46)	PEDOT	Not detected
		H ₂ SO ₄	63		H ₂ SO ₄	66
		Amberlyst	12		Amberlyst	44
2,7	 (38)	PEDOT	70	 (37)	PEDOT	83
		H ₂ SO ₄	48		H ₂ SO ₄	53
		Amberlyst	40		Amberlyst	48
3,8	 (33)	PEDOT	91	 (40)	PEDOT	Not Detected
		H ₂ SO ₄	85		H ₂ SO ₄	Not Detected
		Amberlyst	70		Amberlyst	Not Detected
4,9	 (36)	PEDOT	<1	 (41)	PEDOT	Not Detected
		H ₂ SO ₄	87		H ₂ SO ₄	<1
		Amberlyst	96		Amberlyst	<1
5,10	 (45)	PEDOT	Not Detected	 (39)	PEDOT	Not detected
		H ₂ SO ₄	14		H ₂ SO ₄	18
		Amberlyst	<1		Amberlyst	<1

Stoichiometric Attempts:

Given that reactions with a variety of nitriles were desired to further determine the scope of the PEDOT-mediated Ritter reactions, it was necessary to find a non-nitrile solvent. A solvent study was performed in which acetone, THF, p-dioxane, 1,2-dichloroethane, and nitromethane were tested for their suitability in the Ritter reaction (Table 2).

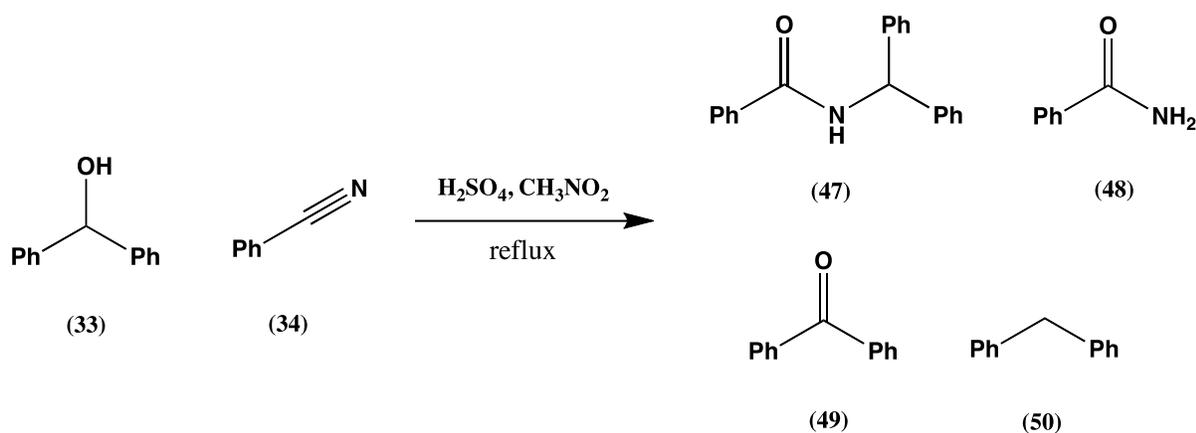
Table 2: Solvent Boiling Points

Entry	Solvent	Boiling Point
1	acetone	56 °C
2	THF	65-67 °C
3	p-dioxane	100-102 °C
4	1,2-dichloroethane	83 °C
5	nitromethane	101.2 °C
6	acetonitrile	81-82 °C
7	toluene	110-111 °C
8	benzene	80 °C

Acetone and THF showed no observable reaction by GCMS, which is presumably because of their low boiling points (Table 2, entries 1 and 2). The use of p-dioxane furnished an unknown product, which is believed to be the result of an interaction between the alcohol and the solvent. The use of 1,2-dichloroethane resulted in a failed reaction and the recovered PEDOT also failed to show conversion in a separate reaction in acetonitrile. It is unclear how this deactivation took place; however, it was clear that 1,2-dichloroethane could not be used as a solvent. Finally, nitromethane allowed for successful performance of the PEDOT-mediated Ritter reaction. An interest was taken in nitromethane based on the Friedel-Crafts alkylation that was previously done in toluene in benzene. As previously mentioned, toluene, which is the higher boiling solvent of the two (Table 2, entries 7 and 8), showed a higher consumption of the starting material than benzene. It follows that nitromethane, with a

similar boiling to toluene (Table 2, entry 5), should show a higher consumption of starting material than the lower boiling acetonitrile (Table 2, entry 6). Unlike toluene, however, nitromethane will not interact with the materials being used in the Ritter reaction.

We attempted to optimize a stoichiometric ratio of nitrile to alcohol with benzonitrile and diphenylmethanol in nitromethane. As seen in Scheme 12 and Table 3, the desired amide product (**47**) was furnished, along with the undesired amide (**48**), oxidation (**49**), and dehydration (**50**). The results using PEDOT were compared with sulfuric acid, given that it is a more traditional mediator.



Scheme 12: Stoichiometric Ritter reaction

Although the PEDOT yields remain unoptimized, this was the first instance in which we were able to show that PEDOT can be used as a mediator in Ritter reactions of alcohols and nitriles in non-nitrile solvents. It was surprising to note that the oxidation product became the major product in the 2.0 eq. case and the cause of this outcome remains unknown. When the equivalence of nitrile is increased to 5.0 eq., a shift of the major product to the desired amide is seen, although at significantly lower yield (22%) compared to sulfuric acid (Table 3, entries 3, 4, and 5). Of particular interest is the fact that PEDOT yielded significantly less

nitrile hydrolysis to the primary amide compared to sulfuric acid, which is strongly indicative of PEDOT's ability to mediate reactions under mild conditions.¹⁶

Table 3: Results summarizing stoichiometric Ritter reactions between diphenylmethanol and benzonitrile mediated by PEDOT and H₂SO₄

Entry	Conditions	Isolated Yield Percent			
		47	48	49	50
1	2.0 eq. H ₂ SO ₄ 2.0 eq. PhCN	46	75	4	1
2	2.0 eq. H ₂ SO ₄ 2.5 eq. PhCN	79	21	trace	trace
3	2.0 eq. H ₂ SO ₄ 5.0 eq. PhCN	88	38	trace	ND
4	PEDOT 2.0 eq. PhCN	8	12	35	8
5	PEDOT 5.0 eq. PhCN	22	6	20	6

PEDOT-Mediated Ritter Reactions with Various Nitriles:

As previously mentioned, it was desirable to perform reactions with a variety of nitriles in order to broaden the understanding of the scope of the PEDOT-mediated reactions. Individual reactions have been performed between benzyl alcohol and diphenylmethanol with acrylonitrile (**51**), cyclohexanecarbonitrile (**52**), and trimethylacetoneitrile (**53**) (Figure 9).

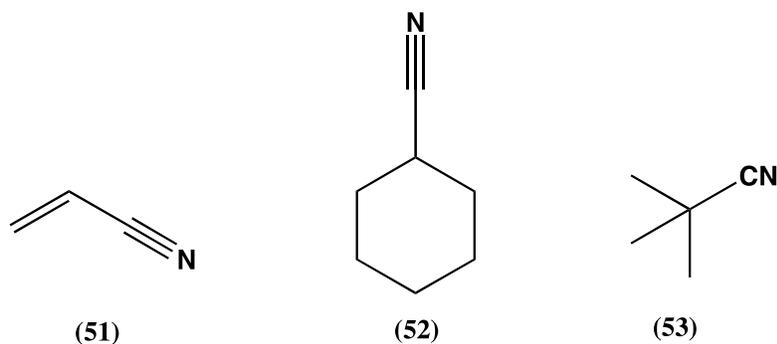


Figure 9: From left to right, acrylonitrile, cyclohexanecarbonitrile, and trimethylacetoneitrile

To date, these reactions have mostly shown only significant yields of the major byproduct, which is believed to be the ether byproduct. However, what is important to note are the reactions done between benzyl alcohol and trimethylacetone nitrile.

When this reaction was first performed, the nitrile and alcohol were added to the reaction at the same time and results observed via GCMS indicated that there was more ether byproduct than desired *N*-benzylacetamide product (Figure 10). When this

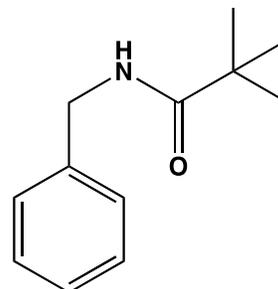


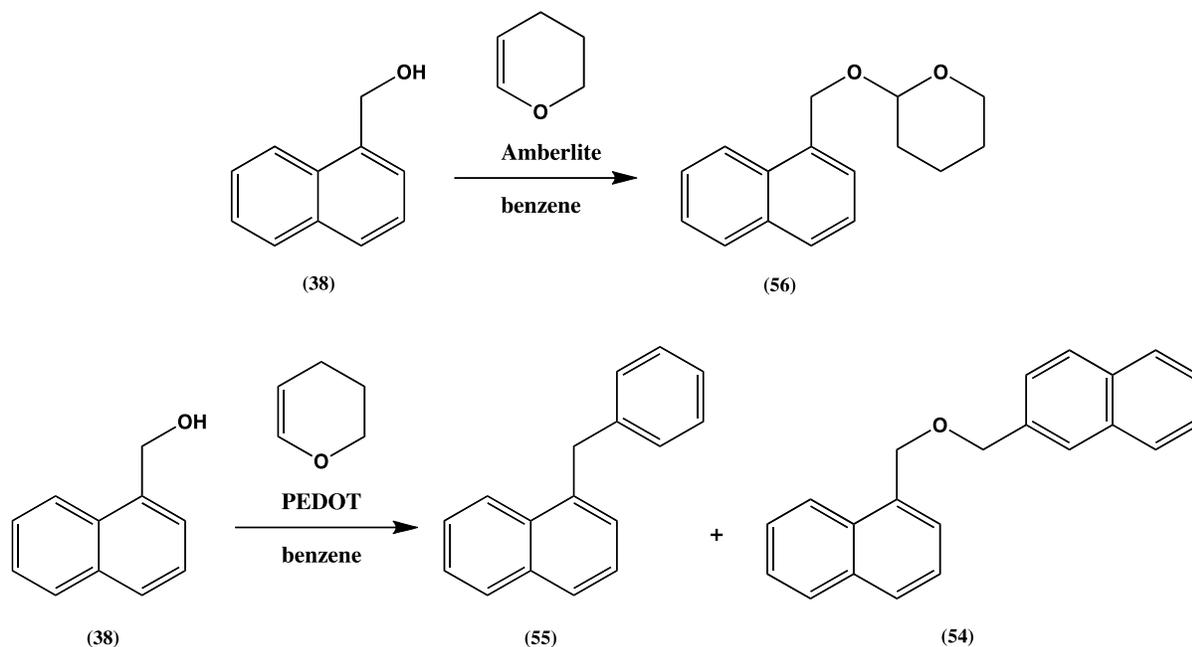
Figure 10: *N*-benzylacetamide

reaction was performed a second time, the addition was slowed down using an addition funnel so that benzyl alcohol in nitromethane could be added dropwise to the reaction at a rate of ~14 seconds per drop. In this case, GCMS results showed a shift to the amide as the major product with significant amounts of the ether byproduct still remaining. Furthermore, GCMS analysis immediately after the addition was complete indicated the presence of alcohol, which suggests that 14 seconds is not enough time for a drop of alcohol to be completely consumed. It is noteworthy that the slow addition is not a viable option with the sulfuric acid because the sulfuric acid would react with the nitrile throughout the addition of the alcohol.

Mechanistic Studies:

Given that the traditional Ritter reaction can take place with alkenes and halides, it was necessary to determine whether or not the same was true of PEDOT; therefore, individual reactions of styrene and benzyl chloride were attempted in refluxing acetone nitrile. No reaction was observed by GCMS after 2 hours. Previous results have shown that, even in reactions demonstrating poor reactivity, reaction progress would begin within 2 hours. It is

important to note that the PEDOT used in the reaction with benzyl chloride was not reused in another reaction. Based on the deactivation of the PEDOT seen with the 1,2-dichloroethane, it is possible that the same is actually happening with benzyl chloride, which could suggest the loading of chlorine onto the polymer. Additionally, PEDOT seems to preferentially react with alcohols in the presence of alkenes, which can be seen in the attempted tetrahydropyranylation of naphthalenemethanol and 3,4-dihydro-2*H*-pyran in refluxing benzene (Scheme 12). As observed by the GCMS, the major products of this reaction were di-1-naphthylenemethyl ether (**54**) and the Friedel-Crafts alkylation product (**55**) resulting from the reaction of the naphthyl carbocation and benzene showing that PEDOT is reacting with the naphthalenemethanol rather than the pyran. When performing a similar reaction using Amberlite IRE-50(H) (a known polymer-bound acid) as the initiator, the desired tetrahydropyranyl ether (**56**) was observed via GCMS (Scheme 13).



Scheme 13: Tetrahydropyranylation Reactions with Amberlite and PEDOT

The differences between the two mediators not only support PEDOT as an alcohol-selective initiator, but are also strongly indicative of PEDOT not behaving as a polymer-bound acid. The presence of the triflate counter ion in the polymer structure of PEDOT could indicate the triflic acid is mediating these reactions; however, the above results indicate otherwise. Again, because of the similar functionality of Amberlyst and triflic acid as opposed to Amberlite and triflic acid, it may be important to try a similar set of reactions using Amberlyst instead of Amberlite and note whether or not any changes take place.

Interestingly, after a PEDOT-mediated Ritter reaction with triphenylmethanol, as observed by GCMS, only trace amounts of the desired *N*-tritylacetamide product (**57**) were seen, along with the reduction product triphenyl methane (**58**) and small amounts of what appears to be 9-phenylfluorene (**59**) (Figure 11). Similar reactions mediated by sulfuric acid and Amberlyst produced yields of 87% and 96% respectively. These differences suggest that the hydroxyl –OH group may need to directly interact with the PEDOT in order for a reaction to proceed. Traditional acids liberate an electrophilic H⁺, which is more easily approached by the triphenylmethanol, regardless of steric hindrance. In contrast, with PEDOT, being a much larger mediator, triphenylmethanol has much more difficulty in overcoming this steric hindrance, thus, it presents reduced reactivity.

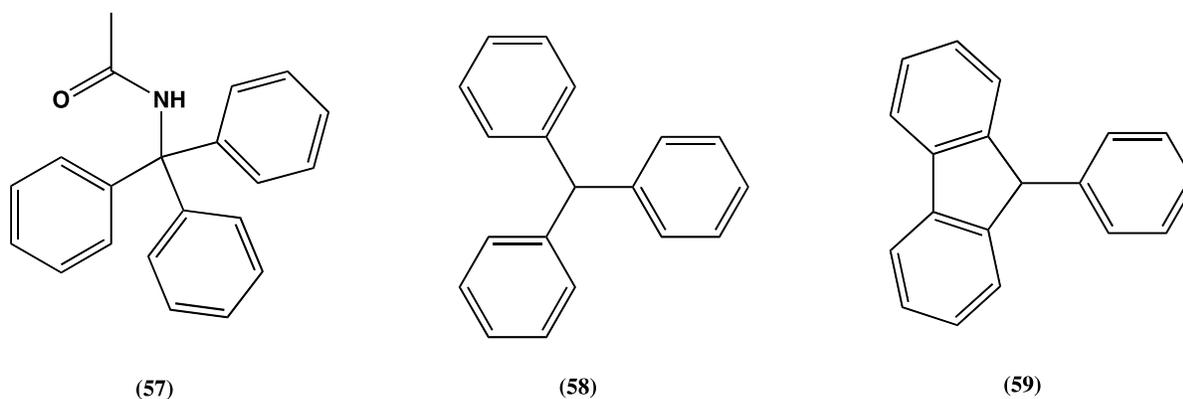


Figure 11: From left to right, *N*-tritylacetamide, triphenyl methane, 9-phenylfluorene

The reaction with 1-adamantanol is a particularly exciting case, which furnished the desired *N*-adamantylacetamide product (Figure 12) in 83% yield with PEDOT and at 53% and 48% with sulfuric acid and Amberlyst respectively. The PEDOT-mediated reaction took far longer (~32 hours) than any other reaction, including those mediated by sulfuric acid and Amberlyst. This observation is consistent with the hypothesis that sterics may hinder the approach of the alcohol to the polymer and further supports this mode of reactivity over one involving the use of an H⁺.

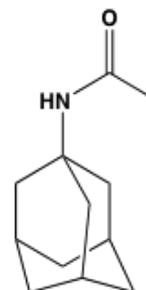


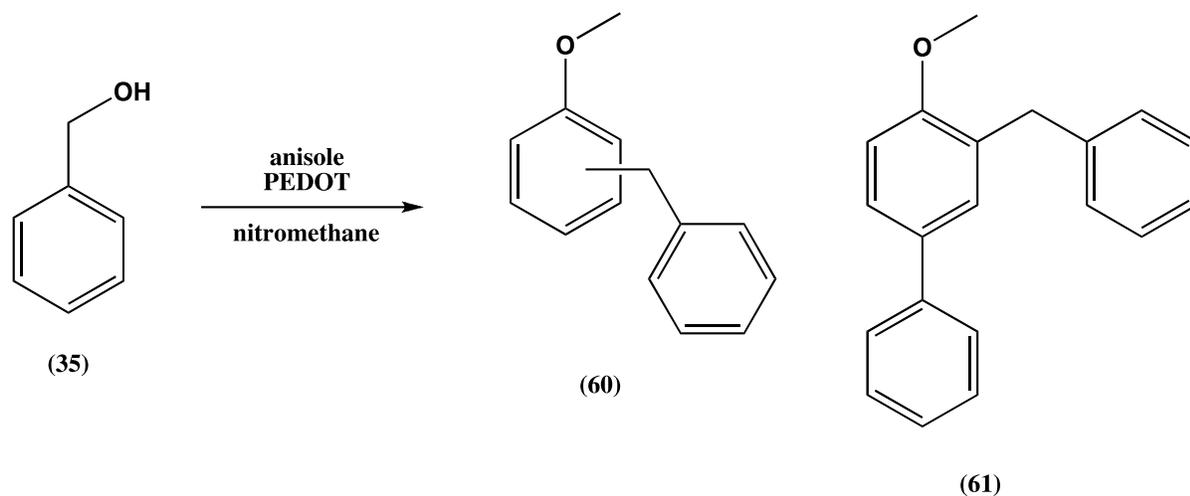
Figure 12: *N*-adamantylacetamide

In an additional study, a 1:1 mixture of naphthalenemethanol and cyclohexanol were reacted with PEDOT in refluxing acetonitrile. In this instance, naphthalenemethyl acetamide and unreacted cyclohexanol along with very small amounts of unreacted naphthalenemethanol were observed. This could indicate that PEDOT will behave selectively under similar reaction conditions, which is of potential importance in total synthesis through the elimination of the need for protection and deprotection steps; however, it may also be attenuated by temperature meaning that cyclohexanol may need higher temperatures before reaction progress can be seen. Additional studies of this reaction must be conducted due to the fact that not all of the cyclohexanol was recovered, meaning that it is possible that an unknown quantity of cyclohexene was produced and not seen via GCMS due to its low boiling point.¹⁶

Other Reactions Mediated by PEDOT:

In addition to the Ritter reaction, our studies have shown that PEDOT can mediate Friedel-Crafts alkylations in a non-aromatic solvent (Scheme 14), as well as enol alkylations

(Scheme 15). While it is true that PEDOT was previously reported to mediate Friedel-Crafts alkylations, the difference here lies in our ability to perform these reactions with a stoichiometric amount of the aromatic reagent, in this case anisole, in nitromethane. Previously, PEDOT-mediated Friedel-Crafts alkylations had only been performed using the aromatic compound as both the reagent and the solvent. This is profoundly interesting because this indicates that Friedel-Crafts alkylations can be done at high yields in non-aromatic solvents, increasing the synthetic utility of this process. Unfortunately, the results of the Friedel-Crafts alkylation may also indicate that our reactions with nitriles may never be high yielding. When the former was performed, the desired alkylation product (**60**) was furnished along with what appears to be a di-substituted byproduct (**61**) (Scheme 14). No ether byproduct was formed suggesting that the anisole is nucleophilic enough that it will attack and form the desired product before the ether byproduct can be formed.

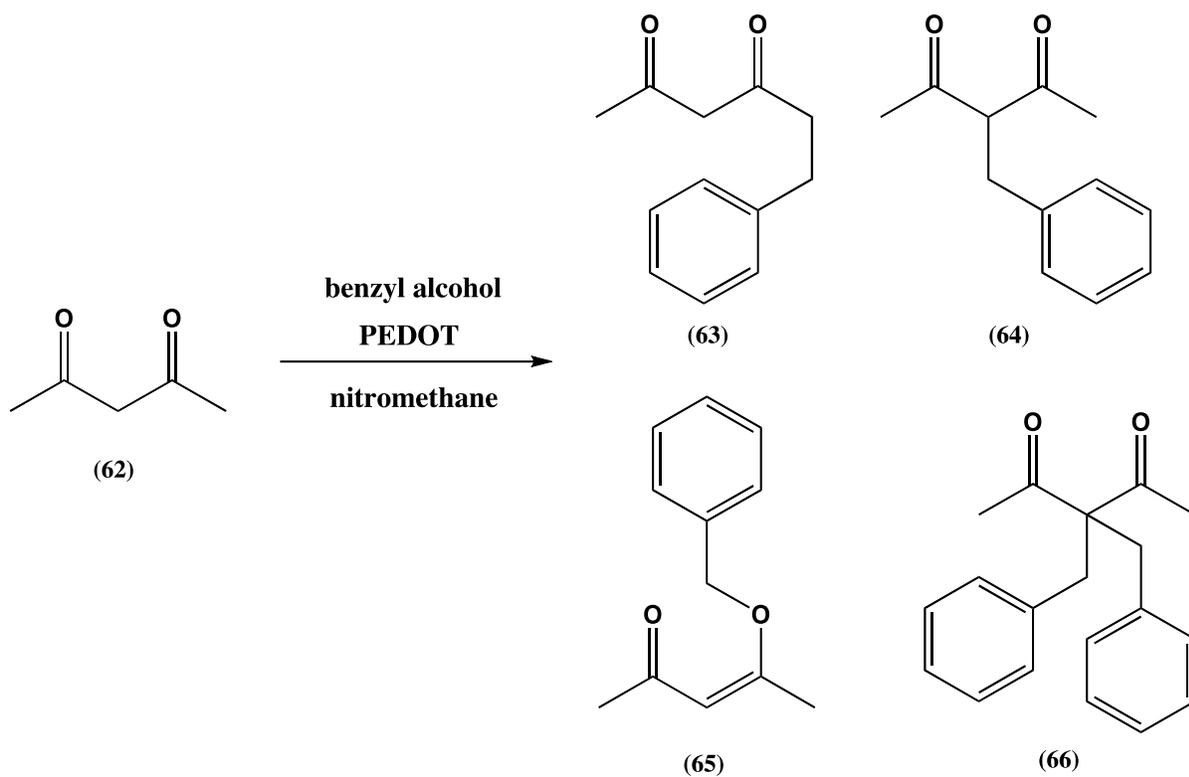


Scheme 14: Friedel-Crafts Alkylation in Nitromethane

In the reactions with nitriles, we see significant amounts of ether byproduct formation, which may suggest that the nitriles are not nucleophilic enough to overcome the formation of the

ether byproduct; therefore, we may continue to maintain an unfortunately low ceiling for amide formation.

An enol alkylation utilizing 2,4-pentanedione (**62**) with benzyl alcohol and PEDOT in nitromethane was also performed furnishing a mixture of at least two of three alkylated products (**63-65**) and small amounts of an unidentified di-alkylated byproduct (**66**). Like the Friedel-Crafts alkylation, no ether byproduct was observed (Scheme 15).



Scheme 15: Enol Alkylation in Nitromethane

EXPERIMENTAL

General Considerations:

Most starting materials and solvents were used as received from commercial sources without further purification; however, initial naphthalenemethanol was prepared in house by way of a sodium borohydride reduction. Proton Nuclear Magnetic Resonance ($^1\text{H-NMR}$) spectra were obtained on a Bruker-DRK300 (300 MHz). Chemical shifts are reported in ppm downfield and were internally referenced using CDCl_3 (7.26 ppm) or DMSO-d_6 (2.50 ppm) as a solvent. Proton NMR data are reported by chemical shift (multiplicity, coupling constants in Hz, number of protons). Multiplicity was abbreviated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of a doublet), dt (doublet of triplets), br s (broad singlet), br d (broad doublet). Carbon-13 Nuclear Magnetic Resonance ($^{13}\text{C-NMR}$) spectra were obtained on a Bruker DRX-300 (75 MHz). Chemical shifts are reported in ppm downfield and were internally referenced using CDCl_3 (77.2 ppm) or DMSO-d_6 (39.5 ppm) as a solvent. Gas chromatography-mass spectroscopy (GC-MS) spectra were acquired on either an HP 6890 Series GC with a 5973 Mass Selective Detector or an HP 5890 Series II GC with a 5971 Mass Selective Detector and are abbreviated as EI (electrospray)

Preparation of Poly-(3,4-ethylenedioxythiophene):

To an electrochemical cell with two metal plates serving as working and counter electrodes was added a 23.4 mM solution of 3,4-ethylenedioxythiophene (10 mL, 93.6 mmol) and 0.1 M lithium triflate in 4 L acetonitrile. Traditionally, 10 mM solutions of monomers are utilized for electropolymerizations.¹⁶ Electropolymerizations were done at +1.3 V for 3000 seconds using chronoamperometry. The PEDOT-coated working electrode was washed

with acetonitrile before being scraped. The collected PEDOT (~11 g, 82.6%) was vacuum dried.

General Method A – Ritter Reactions Mediated by PEDOT with Acetonitrile as Solvent:

To a round bottom flask charged with 25 mL acetonitrile and the alcohol (1.00 mmol) was added PEDOT (0.200 g). The reaction was stirred at reflux until no further alcohol consumption was observed via GCMS before being filtered and concentrated *in vacuo* to obtain the crude products, which were purified by flash chromatography when necessary.

General Method B – Stoichiometric Ritter Reactions Mediated by PEDOT with Nitromethane as Solvent:

To a round bottom flask charged with 25 mL nitromethane, the alcohol (1.00 mmol), and the nitrile (1.00 mmol) were added PEDOT (0.200 g). The reaction was stirred at reflux until the alcohol was consumed as observed via GCMS. The reaction was filtered and concentrated *in vacuo* to obtain the crude products.

Analysis of PEDOT:

The analysis of PEDOT before and after it is utilized in chemical reactions is desirable for acquiring knowledge of its mechanism. To date, PEDOT has only been analyzed by Infrared Spectroscopy (IR), which provided no significant conclusions about the mechanism of the PEDOT-mediated Ritter reactions. Additional instrumentation, such as a Scanning Electron Microscope (SEM) will be used in the future.

***N*-benzylacetamide (4a):** $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.38-7.22 (m, 5H), 5.94 (br s, 1H), 4.41 (d, $J = 5.7$ Hz, 2H), 2.00 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 170.3, 138.3, 128.6, 127.8, 127.4, 43.6, 23.1; MS (EI): $m/z = 149$ (M^+)

***N*-(naphthalene-1-ylmethyl)acetamide (4b):**

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 8.00 (d, $J = 8.4$ Hz, 1H), 7.87 (dd, $J = 6.6, 2.2$ Hz, 1H), 7.81 (t, $J = 4.8$ Hz, 1H), 7.53 (m, 2H), 7.41 (d, $J = 5.2$ Hz, 2H), 5.89 (br s, 1H), 4.84 (d, $J = 5.3$ Hz, 2H), 1.97 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 170.3, 134.3, 133.9, 131.8, 129.2, 129.1, 127.3, 127.1, 126.5, 125.8, 124.0, 42.3, 23.6; MS (EI): $m/z = 199$ (M^+)

***N*-benzhydrylacetamide (4c):** $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.36-7.20 (m, 10H), 6.32 (br d, $J = 8.1$ Hz, 1H), 6.23 (d, $J = 8.1$ Hz, 1H), 2.01 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 169.4, 141.6, 128.9, 127.4, 127.5, 57.0, 23.2; MS (EI): $m/z = 225$ (M^+)

***N*-tritylacetamide (4d):**

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 7.46-7.20 (m, 15H), 6.64 (br s, 1H), 2.12 (s, 3H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 169.2, 144.8, 128.8, 128.1, 127.2, 70.7; MS (EI): $m/z = 301$ (M^+)

***N*-isopropylacetamide (4e):**

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.42 (br s, 1H), 4.05 (m, 1H), 1.93 (s, 3H), 1.13 (d, $J = 6.5$ Hz, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 169.3, 41.5, 23.7, 22.9; MS (EI): $m/z = 101$ (M^+)

***N*-(*tert*-butyl)acetamide (4f):**

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.40 (br s, 1H), 1.89 (s, 3H), 1.32 (s, 9H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 169.8, 50.8, 28.5, 24.1; MS (EI): $m/z = 115$ (M^+)

***N*-adamantylacetamide (4g):** $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 5.15 (br s, 1H), 2.06 (s, 3H), 1.98 (s, 6H), 1.89 (s, 3H), 1.66 (s, 6H); $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 169.5, 51.7, 41.5, 36.3, 29.4, 24.6; MS (EI): $m/z = 193$ (M^+)

***N*-cyclohexylacetamide (4j):**

¹H-NMR (300 MHz, CDCl₃): δ 5.72 (br s, 1H), 3.70 (m, 1H), 1.94-1.81 (m, 4H), 1.72-1.51 (m, 3H), 1.39-1.00 (m, 6H); ¹³C-NMR (75 MHz, CDCl₃): δ 169.3, 48.3, 33.2, 25.6, 25.0, 23.6, MS (EI): *m/z* = 141 (M⁺)

***N*-benzhydrylbenzamide (6):** ¹H-NMR (300 MHz, CDCl₃): δ 7.85-7.80 (m, 2H), 7.56-7.27 (m, 13H), 6.69 (br d, *J* = 7.7 Hz, 1H), 6.46 (d, *J* = 7.7 Hz, 1H); ¹³C-NMR (75 MHz, CDCl₃): δ 166.6, 141.5, 134.3, 131.9, 128.9, 128.7, 127.7, 127.6, 127.2, 57.6; MS (EI): *m/z* = 287 (M⁺)

CONCLUSIONS AND FUTURE WORK

We have shown that the conducting polymer PEDOT can mediate Ritter reactions between activated alcohols and nitriles. In addition, PEDOT has been shown to mediate Friedel-Crafts alkylations with stoichiometric amounts of the aromatic substituent in addition to mediating enol alkylations. Although the mechanism of PEDOT remains unclear, the work reported supports the premise that PEDOT is behaving as an alcohol-selective Lewis acid. In addition, the absence of reactivity with styrene along with the results of the tetrahydropyranylation suggest that PEDOT-mediated reactions are not being mediated by putative amounts of triflic acid bound to the polymer or generated *in situ*. The hypothesis that PEDOT behaves as a Lewis acid is further supported by the slow reaction time seen in the reaction with adamantanol and in the seeming lack of reactivity with triphenylmethanol, both of which could be the result of a steric effect.

Ongoing investigation into the mechanism remains of interest due to its synthetic importance and potential benefit in the creation of a new generation of low cost, reactive conducting polymers. In the future, analysis of the polymer will be explored before and after reactions in an attempt to note changes in the structure or molecular weight and derive knowledge about the mechanism.

Additionally, efforts to increase the yields of the PEDOT-mediated stoichiometric Ritter reaction are ongoing. To date, we have shown that slowing down the addition of benzyl alcohol to a reaction containing trimethylacetonitrile shifts the major product to the desired N-benzylethanamide product. However, a significant amount of ether byproduct still remains and it is desirable to decrease this yield, while simultaneously increasing the yield of our desired product.

Finally, given that there are a vast number of reactions of alcohols and PEDOT has already been shown to successfully mediate a variety of reactions of alcohols, we will continue to explore the use of PEDOT in other acid-mediated reactions of alcohols.

APPENDIX A: LIST OF COMPOUNDS

- (1) *N*-carboxamides
- (2) nitriles
- (3) carbocations
- (4) lactams
- (5) oxazolines
- (6) dihydroisoquinolines
- (7) (-)-4-epiixinyssamine
- (8) axynissamine
- (9) Key olefinic intermediate in the synthesis of (-)-4-epiixinyssamine
- (10) chloroacetamide
- (11) General primary, secondary, and tertiary alcohols
- (12) protic acids
- (13) Elimination of water
- (14) alkyl halides
- (15) alkenes
- (16) nitrilium ion
- (17) imidate
- (18) Hydrated intermediate in the mechanism of the Ritter reaction
- (20) Desired amide product of Ritter reactions
- (21) Tetrahydropyranylation products
- (22) 3,4-dihydro-2*H*-pyran
- (23) ester

- (24) nitrobenzene
- (25) aniline
- (26) Oxidation product from reaction using polypyrrole-based heteropoly acid catalyst
- (28) hydrogen peroxide
- (29) homoethers
- (30) aldehyde from PEDOT-mediated oxidation reaction
- (31) Cyclodehydration products
- (32) acyclic sugars
- (33) diphenylmethanol
- (34) benzonitrile
- (35) benzyl alcohol
- (36) triphenylmethanol
- (37) adamantanol
- (38) naphthalenemethanol
- (39) cyclohexanol
- (40) isobutyl alcohol
- (41) 1-butanol
- (42) benzyl acetate
- (43) isobutyl acetate
- (44) butyl acetate
- (45) isopropyl alcohol
- (46) *tert*-butanol
- (47) Desired amide product of stoichiometric Ritter reaction

- (48) Undesired amide byproduct of stoichiometric Ritter reaction
- (49) Oxidation byproduct of stoichiometric Ritter reaction
- (50) Dehydration product of stoichiometric Ritter reaction
- (51) acrylonitrile
- (52) cyclohexanecarbonitrile
- (53) trimethylacetoneitrile
- (54) di-1-naphthylenemethyl ether
- (55) Friedel-Crafts alkylation product from attempted tetrahydropyranylation with PEDOT
- (56) Tetrahydropyranyl ether
- (57) *N*-tritylacetamide
- (58) triphenyl methane
- (59) 9-phenylfluorene
- (60) Desired alkylation product from Friedel-Crafts alkylation mediated by PEDOT in nitromethane
- (61) di-substituted byproduct from Friedel-Crafts alkylation mediated by PEDOT in nitromethane
- (62) 2,4-pentanedione
- (63) Alkylation product from enol alkylation mediated by PEDOT in nitromethane
- (64) Alkylation product from enol alkylation mediated by PEDOT in nitromethane
- (65) Alkylation product from enol alkylation mediated by PEDOT in nitromethane
- (66) Di-alkylated byproduct from enol alkylation mediated by PEDOT in nitromethane
- (Figure 1) PEDOT polymerized around living neural cells
- (Figure 2) Poly-(3,4-ethylenedioxy thiophene) (PEDOT)

(Figure 3) styrene

(Figure 4) benzyl Chloride

(Figure 5) cyclohexene

(Figure 6) From left to right, benzyl acetate, isobutyl acetate, and butyl acetate

(Figure 7) *N*-(naphthalen-1-ylmethyl)ethanamide

(Figure 8) *N*-benzhydrylethanamide

(Figure 9) From left to right, acrylonitrile, cyclohexanecarbonitrile, and trimethylacetone

(Figure 10) *N*-benzylacetamide

(Figure 11) From left to right, *N*-tritylacetamide, triphenyl methane, and 9-phenylfluorene

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