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Ionic Liquid Mediated Synthesis of Thiophene Analogues

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Abstract:
A simple, inexpensive and efficient synthesis of 2,3,4-tri substituted thiophene derivatives under mild and solvent free condition is reported using ionic liquid with excellent yields. This methodology provides easy quantitative access to various functionalized derivatives using commercially available choline chloride and urea as catalyst.

Keywords*: Thiophene, ionic liquid, β-oxodithioesters, acetylenedicarboxylate, ionic liquids, urea, solvent free condition*

1. Introduction

Substituted thiophenes have emerged as a class of important heterocycles because of their presence in a broad spectrum of natural and synthetic molecule.[1-2]Thiophene have significant with potential application as organic semiconductor,[3]organic light emitting diodes(OLEDS),[4] organic field effect transistors (OFETs),[5] lasers,[6] sensors and photovoltaic cells.[7]

Moreover, thiophenes have significant biological applications the blockbuster drug Plavix is a potent antiplatelet agent used in the treatment of coronary artery disease.[8]Articaine is the most commonly used dental anesthetic in Europe;[9] and PaTrin-2 is an inhibitor of the DNA repair enzyme *o*-methylguanine-DNA methyl transferase with potential to increase the effectiveness of alkylating agents as cancer therapeutics (Figure 1).[10]

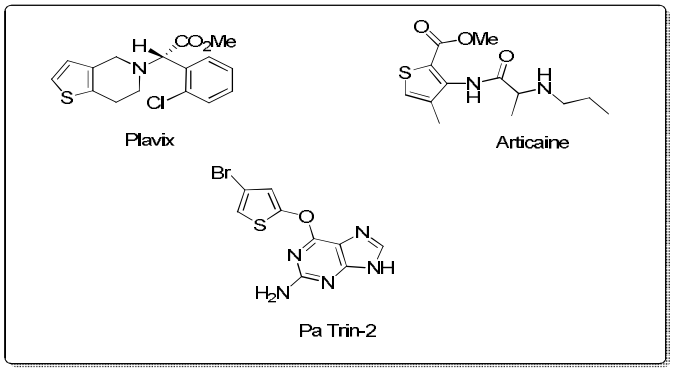
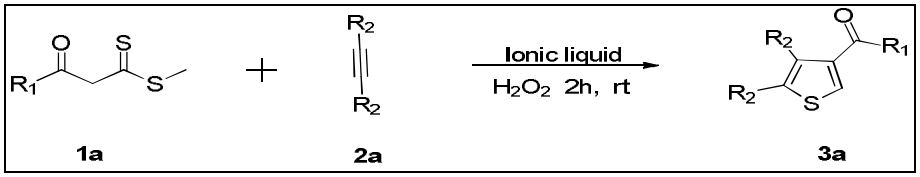


Figure 1: Some biologically importance thiophene molecules

The general synthetic approaches to such thia-heterocycles involve either the functionalization in the α- and β-position of the preconstructed thiophene skeleton,[11]or the construction of the thiophene ring from appropriately substituted open chainprecursors.[12]Although these methods are very useful for the synthesis of thiophene but the reactions involved have major limitations such as expensive reagents, lengthy reaction times, high temperature requirement and also tedious work-up procedures. Therefore, the development of novel method to overcome the limitations for the synthesis of 2,3,4-tri substituted thiopheneis of great importance because of their biological and pharmaceutical importance. Over the past decade utility of ionic liquids in catalysis and as deep eutectic solvent for various synthetic processes has been well recognized by the chemists all over the world. Due to their chemical properties, such as recyclability, negligible vapor pressure, ability to dissolve wide range of substrates and catalysts, thermal stability. Ionic liquids have been considered as viable alternatives to the conventional volatile organic solvents.[13-16]Protic and Bronsted basic liquids, in particular, have received increasing attention for carrying out organic transformations as they can replace volatile organic solvents as well as highly acidic catalytic systems.[17-18]Hence,the use of ionic

liquids have been found to be advantageous as they usually involve in simple reaction processes as compared to most of the traditional methods.

β-oxodithioesters, which were not sourced were preparedaccording to reported procedure.[19]The utility of β-oxodithioestersas versatile intermediate in organic synthesis has been well recognized.[20-21]In continuation of our efforts in the development of novel, environ-friendly and synthetic methodologies,[22-29] and with the aim to diverse a more general synthetic route for heterocycles. We were explored the tri substituted thiophenevia basic ionic liquid using β-oxodithioester and dialkylacetalynedicarboxylate. Thus when β-oxodithioester1a were treated with dialkylacetalynedicarboxylate2a and H_2O_2in basic ionic liquid in at room temperature for 2h the corresponding 2,3,4-tri substituted thiophene3a were obtained with good yield (scheme 1).



Scheme 1: Synthesis of 2,3,4-tri substituted thiophene derivatives

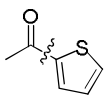
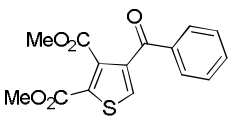
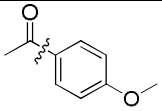
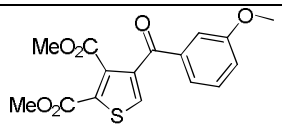
Entry	Solvent	H_2O_2	Reaction time (h)	Yield (%)[b]
1	Choline chloride:urea	-	24	no product
2	Choline chloride:urea	1	24	20
3	$ZnCl_2$:Choline chloride	1	24	Traces
4	Choline chloride:urea	1.5	12	50
5	Choline chloride:urea	2.5	2	76
6	Choline chloride:urea	3.0	3	74
7	$ZnCl_2$:Choline chloride	2.5	12	30

Table 1: Ionic liquid mediated synthesis of 2,3,4-tri substituted thiophenes[a]

[a] All reaction were carried out usingβ-oxodithioester (1 eq), dimethyl acetylenedicarboxylate(1.5 eq), H_2O_2(2.5 eq)[b] yield obtained after column chromatography.

2. Result and Discussion

In order to explore the scope and optimal conditions (Table 1).Ionic liquid catalyzed synthesis of thiophene**3a** was selected as a model. The reaction of β-oxodithioester**1a**dimethyl acetylenedicarboxylate**2a** and H_2O_2 at room temperature in presence of ionic liquid and different equivalence of H_2O_2 are summarized in Table 1.Initially we attempted the reaction of β-oxodithioester**1a** with dimethyl acetylenedicarboxylate**2a** in basic ionic liquid (choline chloride- urea) at room temperature for 24hdesired product was not observed.The same was carried out with H_2O_2 for 24 h 20 % yield was observed.Same reaction also conducted in acidic ionic liquid, desired product was not observed.Upon increasing the equivalent of H_2O_2, the formation of product was improved(Table 1, entry 4). At 2.5 equiv of $H_2O_2$the yield was 76% (Table 1, entry 5). These results suggest that H_2O_2played a vital role indehydrogenationof the reaction. Using the optimized reactionconditions (Table 1, entry 5), we subsequently explored the reaction scope by using dialkylacetylenedicarboxylate and using β-oxodithioester to afford 2,3,4- tri substituted thiophene products in 72-80% yield (Table 2).

Entry	R2	R1	Compound structure	Time in h	Yield [a]
1	CO_2Me			2	76
2	CO_2Me			2	79

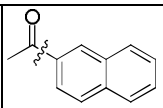
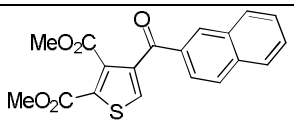
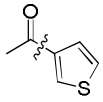
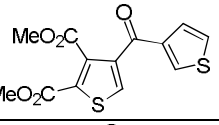
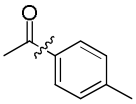
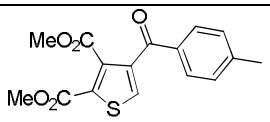
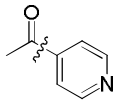
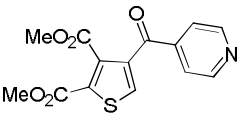
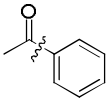
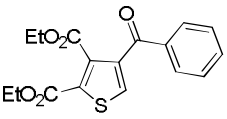
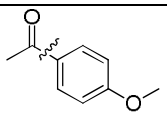
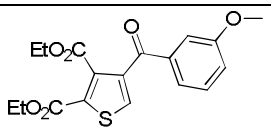
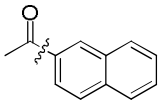
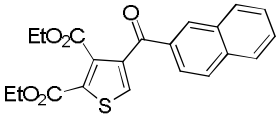
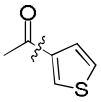
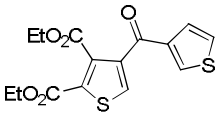
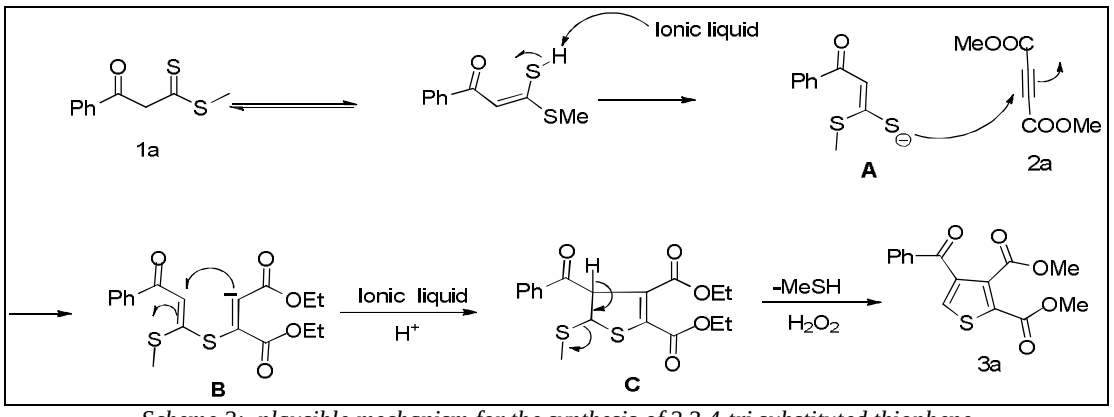
3	CO_2Me			2	75
4	CO_2Me			2	73
5	CO_2Me			2	78
6	CO_2Me			2	72
7	CO_2Et			2	75
8	CO_2Et			2	80
9	CO_2Et			2	77
10	CO_2Et			2	75

Table 2: Tri substituted Synthesis of thiophene derivatives
[a]Isolated yields



Scheme 2: plausible mechanism for the synthesis of 2,3,4-tri substituted thiophene

Mechanistically the formation of 2,3,4-tri substituted thiophene is illustrated in Scheme 2. Basic ionic liquid abstracts a proton of β-oxodithioester1ato generate nucleophilic anion A. Addition of mercapto nucleophilic A to 2,3 dimethyl acetylene

dicarboxylate2a fallowed by intramolecular cyclisation to afford 3,4, dihydrothiopheneC. Further C undergoes H_2O_2 catalysed dehydrogenation with the elimination of MeSH to give 2,3,4,tri substituted thiophene3a

In conclusion we have developed a simple and environmentally benign procedure for the synthesis of 2,3,4-tri substituted thiophene using β-oxodithioester and dialkylacetylenedicarboxylate in basic ionic liquid, via neucliophilic and intra molecular cyclisation with elimination of MeSH, this offers several advantage such as good yield, simple procedure, low cost,short reaction times, mild condition and useful for library synthesis in industries.

3. Experimental

3.1. Materials and Methods

All work relating to analytical thin layer chromatography were performed with E. Merck silica gel $60F_{254}$ aluminum plates and were visualized with UV light. The following mobile phases were employed for TLC: chloroform, methanol and hexane, and ethyl acetate in different ratios. The instrumental techniques employed for the characterization of the newly synthesized compounds include ^1H and ^{13}C NMR and mass spectroscopy. ^1H and ^{13}C NMR spectra were recorded on a Bruker WM ((400 and 300 MHz) Fourier transforms spectrophotometer in $CDCl_3$ or DMSO-d_6 solution using tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in ppm relative to TMS. Mass and purity were recorded on a LC–MSD-Trap-XCT (Agilent technologies Inc). All the reagents and chemicals used were from sigma Aldrich chemicals.

4. Preparation of Ionic Liquid

A mixture of anhydrous choline chloride (5 g, 35.8 mmol) & anhydrous urea (4.29 g, 71.61 mmol) under nitrogen atmosphere were heated to 50-100 ^oC for30 to 45 minutes with stirring. After the formation of clear viscous liquid (ionic liquid), the reaction mixture was brought to room temperature, this room temperature ionic liquid was used forthe reaction.

- **In a typical experimental procedure:** The β-oxodithioester(0.2g, 0.952 mol) was taken in above prepared ionic liquid & stirred for 5 minutes under nitrogen atmosphere & then dimethyl acetylene dicarboxylate (0.202 g, 1.428 mol) and H_2O_2(0.080g, 2.38 mol) was added & the reaction mixture was stirred at room temperature for 2h under nitrogen atmosphere.Reaction completion was monitored by TLC. Product was with EtOAc. The combined organic layer was washed with water, and saturated brine solution followed by the drying with anhydrous Na_2SO_4. The combined organic layer was evaporated under reduced pressure and the resulting crude product was purified by column chromatography with EtOAc in hexane as eluentwhich afforded the desired product. The products were identified by ^1H NMR, ^{13}C NMR and LCMS, showed good agreement with the assigned structures.

5. Acknowledgement

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6. Supporting information available

Relevant spectra ^1H NMR, ^{13}C NMR and LCMS spectrafor all compounds.

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