

Non-Acidic Mediated Friedel-Craft Reaction of Thiophene Using EtAlCl₂

HALIL ÜNVER, MUTLUHAN BIYIKOGLU and ADNAN BULUT*

Department of Chemistry, Kirikkale University, 71450 Kirikkale, Turkey

*Corresponding author: Fax: +90 318 3572461; Tel: +90 318 3574242; E-mail: adnnblt@kku.edu.tr

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Since alkyl Lewis acids are Brønsted bases, they give a non-acidic reaction media. In this context, acylation of thiophene is investigated in the presence of $EtAlCl_2$ and non-acidic media. Besides 8 examples of thiophene, one example for pyrrole is synthesized in moderate to high yields (up to 99 %).

Key Words: Thiophene, Acylation, Alkyl Lewis acid, Electrophilic aromatic substitution.

INTRODUCTION

Electrophilic aromatic substitution (EAS) is one of the most used methods for obtaining new derivatives of heteroaromatics, which are high electron density of aromatic systems. The Friedel-Crafts acylation followed by a transformation has found a plethora applications in the synthesis of substituted heteroaromatics¹. AlCl₃ is the most common catalyst used for this purpose^{2,3}. FeCl₃⁴, CuFe₂O₄⁵, zeolite⁶ and SnCl₄⁷ are the other catalysts that can be given as examples. Although several catalysts are now available as mentioned above, there have been sustained efforts towards the finding of new catalysts. Recently, Simirnov et al. reported the preparation of 1,4-bis(2thienyl)butane-1,4-dione with SnCl₄, TiCl₄ and AlCl₃ catalysts⁸. Although alkyl Lewis acids are weaker than common Lewis acids (AlCl₃, FeCl₃, etc.), they are also Brønsted bases⁹. Apart from its role as catalyst in the acylation reaction, alkyl Lewis acids were reported to be actively Brønsted base involved in acylation or other reactions^{10,11}. Despite this advantage, their use is rare. To the best of our knowledge, alkyl Lewis acid is used for the first time in the acylation of heteroaromatic compounds (thiophene and furan) in this study.

EXPERIMENTAL

EtAlCl₂ (1 M in hexane) and acyl chlorides were purchased from Aldrich. CH₂Cl₂ was distilled over CaH₂ prior to use. Ethyl acetate and hexane for column chromatography were used without further purification. ¹H and ¹³C NMR were recorded with Bruker Spectroscopin Avance PDX 400 MHz using TMS (tetramethylsilane) as standard. IR spectra were recorded with JASCO FT-IR 480 plus spectrometer and selective peaks are reported. The reactions were monitored by TLC and UV-Lamp. The products were purified with Merck silica gel 5554. The yields are calculated from the isolated products. All spectroscopic data are in good accordance with the literatures.

General procedure for acylation of thiopene: 0.5 mL (0.0063 mol) thiophene and 0.33 mL (0.003 mol) succinyl chloride were dissolved in 20 mL dried CH_2Cl_2 at 0 °C under inert atmosphere. 9.45 mL (0.0095 mol) EtAlCl₂ was added drop by drop to that solution. After mixing 2 h at 0 °C, the mixture was quenched with sat. NH₄Cl and extracted 3 times (total 50 mL) with CH₂Cl₂. The combined organic phase was dried with Na₂SO₄ and concentrated under reduced pressure. Upon purification with flash column (hexane; ethyl acetate, 4;1), the product **3** was isolated (750 mg, 99 % yield).

Methyl(2-thienyl)methanone (1)¹²: ($R_f = 0.24$) ¹H NMR δ 7.69-7.65 (m, 1H), 7.61 (dd, J = 4.9, 1.0 Hz, 1H), 7.13-7.09 (m, 1H), 2.54 (s, 3H). ¹³C NMR δ 189.95, 144.54, 133.45, 132.11, 127.93, 26.76. IR :1660, 1517, 1414, 1356, 1274, 1062, 858, 726, 592.

1,2-*Bis*(**2-thienyl)ethanone** (**2**)¹³: ($R_f = 0.26$) ¹H NMR δ 7.72-7.67 (m, 1H), 7.57-7.51 (m, 1H), 7.15-7.09 (m, 1H), 7.04 (dt, *J* = 6.9, 3.4 Hz, 1H), 6.90-6.82 (m, 2H), 4.28 (s, 2H). ¹³C NMR δ 143.33, 134.04, 132.45, 128.06, 126.90, 126.79, 125.04, 40.23. IR : 1661, 1517, 1414, 1354, 1237, 1059, 856, 700.

1,4-*Bis*(**2-thienyl)butane-1,4-***dione* (**3**)¹³: ($R_f = 0.11$) ¹H NMR δ 7.82-7.66 (m, 2H), 7.55 (dd, *J* = 4.9, 1.0 Hz, 2H), 7.06 (dd, *J* = 4.9, 3.8 Hz, 2H), 3.29 (s, 4H) ¹³C δ 190.7, 143.9, 133.4, 131.9, 127.9, 33.1. IR : 1641, 1545, 1506, 1428, 1360, 1128, 751.

(2-Thienyl)(*p*-tolyl)methanone (4)¹⁴: ($R_f = 0.36$) ¹H NMR δ 7.72 (t, *J* = 13.5 Hz, 2H), 7.64-7.58 (m, 1H), 7.55 (dd, *J* = 3.8, 1.1 Hz, 1H), 7.26-7.18 (m, 2H), 7.07 (dd, *J* = 4.9, 3.8 Hz, 1H), 2.38 (s, 3H). ¹³C NMR δ 135.62, 134.20, 133.37, 129.80, 129.21, 127.74, 21.66. IR : 1704, 1632, 1513, 1413, 1289, 1048, 848, 740.

2-Benzoylthiophene (5)¹⁴: ($R_f = 0.28$) ¹H NMR δ 7.90-7.71 (m, 1H), 7.65-7.57 (m, 1H), 7.52 (dd, J = 3.8, 1.1 Hz, 1H), 7.50-7.43 (m, 1H), 7.41-7.35 (m, 1H), 7.04 (dd, J = 4.9, 3.8 Hz, 1H)). ¹³C NMR δ 187.57, 143.75, 138.20, 135.33, 134.79, 134.21, 132.13, 129.15, 128.34, 127.80. IR : 1627, 1513, 1410, 1288, 1051, 836, 721.

(Z)-1-(2-Thienyl)but-2-en-1-one (6^{15} : (R_f = 0.37) ¹H NMR δ 7.79-7.59 (m, 1H), 7.58-7.36 (m, 1H), 7.16-6.92 (m, 2H), 6.81-6.66 (m, 1H), 1.87 (dd, *J* = 6.9, 1.6 Hz, 3H). ¹³C NMR δ 181.43, 145.13, 143.67, 133.39, 131.54, 128.00, 126.88, 18.32 . IR : 1659, 1614, 1514, 1440, 1415, 1294, 1234, 1063, 907, 784.

1,8-*Bis*(**2-thienyl)octane-1,8-dione** (**7**)¹⁶: ($R_f = 0.15$) ¹H NMR δ 7.70-7.58 (m, 2H), 7.52 (dd, *J* = 4.9, 1.1 Hz, 2H), 7.03 (dd, *J* = 4.9, 3.8 Hz, 2H), 2.87-2.77 (m, 4H), 1.77-1.61 (m, 4H), 1.35 (dt, *J* = 14.1, 5.2 Hz, 4H). ¹³C NMR δ 192.06, 144.08, 132.59, 130.92, 127.41, 38.66, 28.57, 23.99 . IR : 1647, 1411, 1242, 1185, 927, 851, 727.

(Furan-2-yl)(2-thienyl)methanone (8)¹⁷: ($R_f = 0.28$) ¹H NMR δ 8.07 (d, J = 2.4 Hz, 1H), 7.62-7.53 (m, 2H), 7.33-7.25 (m, 1H), 7.07 (dt, J = 3.8, 3.2 Hz, 1H), 6.49 (s, 1H). ¹³C NMR δ 171.60, 151.26, 144.81, 141.14, 132.34, 126.73, 117.20, 111.08. IR; 1622, 1566, 1464, 1413, 1305, 808, 740. IR: 1622, 1566, 1464, 1413, 1305, 1179, 1013, 884, 808.

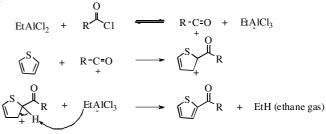
1-(1*H***-Pyrrol-2-yl)ethanone (9)¹⁸:** ($R_f = 0.22$) ¹H NMR δ 6.98 (td, J = 2.8, 1.4 Hz, 1H), 6.81 (ddd, J = 3.8, 2.4, 1.4 Hz, 1H), 6.14 (dt, J = 3.8, 2.4 Hz, 1H), 2.36 (s, 3H). ¹³C NMR δ 187.95, 132.13, 125.43, 117.31, 119.42, 25.53. IR: 1645, 1547, 1428, 1364, 1129, 1045, 841, 773.

RESULTS AND DISCUSSION

Snider and co-workers accomplished many Lewis acid catalyzed reactions using alkyl Lewis acids. They reported that proton-initiated rearrangements do not occur since alkyl Lewis acids give a non-acidic reaction media due to basicity of alkyl parts, which are proton scavengers and rapidly turn into ethane or methane gases¹⁹. When alkyl-acid chlorides are employed in the acylating agent, the formation of acidic proton is thus not to be expected.

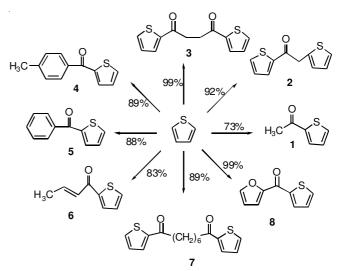
On the other hand, Watt and co-workers reported that acylation of ferrocene with acryloyl chloride would not yield the corresponding unsaturated ferrocenyl ketone, instead afforded propanoyl ferrocene and ferrocenophane derivative using AlCl₃ as a catalyst. They synthesized acryloylferrocene in two steps starting from ferrocene^{19,20}. In first step, 3-chloropropanoylferrocene was obtained through the Friedel-Crafts acylation and in second step, dehydrochlorination of 3-chloropropanoyl ferrocene. However, Dogan and co-workers¹¹ have synthesized acryloylferrocene in one step using EtAlCl₂/ Me₃Al Lewis acids. The aforementioned attributes have prompted us to use EtAlCl₂ as lewis acid in Friedel-Crafts acylation of thiophene.

We speculated that during the acylation of thiophene, ethyl anion abstract the hydrogen form thiophene during the aromatization or after the aromatization (**Scheme-I**). It is clear that the reaction media is non-acidic because ethyl anion have neutralized the proton produced during the acylation.



Scheme-I: EtAlCl₂ as Brønsted base in E_AS reaction

Among eight derivatives of thiophene synthesized (**Scheme-II**), 1,4-*bis*(2-thienyl) butane-1,4-dione (**3**) is the most commonly used one because it is the precursor for SNS type conductive polymers^{2,21}. Therefore, we searched the optimization condition for **3**. The best yield observed was 0.15 M of succinyl chloride and 0.315 M of thiophene were used. On the other hand, the catalyst loading showed that the highest yield obtained when 1.5 equivalent of EtAlCl₂ was used in accord with thiophene.



Scheme-II: Thiophene derivative syntheses in the presence of EtAlCl₂

Different routes are available leading to 1,4-*bis*(2-thienyl)butane-1,4-dione (**3**)²²⁻²⁴. Among these methods, the Friedel-Craft reaction, which is the first reported by Merz and Ellenger albeit with long reaction period (24 h), is mostly used²⁵. Recently, the reaction time has been reduced under forcing conditions (reflux)²¹.

High yields were observed for (furan-2-yl)(2-thienyl)methanone (8) and succinylthiophene (3) (99 % for each) while the lowest yield (73 %) was obtained for acetyl thiophene (1) (Scheme-II). Even in the case of more long substrates, such as suberoylthiophene (7) and crotonoylthiophene (6) good yields (up to 89) were obtained. Our protocol can be extended to the acylation of other aromatics. For this purpose, 1-(1*H*pyrrole-2-yl)ethanone (9) was synthesized with the yield of 90 %. Unfortunately, acylation of pyridine and pyrrole with $EtAlCl_2$ catalyst did not give any products. The reason for this unreactivity may come from the reluctance of pyridine towards the E_AS reactions and acidic proton of pyrrole.

Conclusion

In summary, 8 derivatives of thiophene were synthesized *via* electrophilic aromatic substitution rection in the presence of EtAlCl₂. The yields are in moderate to good yields. The success of the reaction was probably due to the Brønsted basicity of EtAlCl₂. Easy work-up and short reaction period can be said as other advantages over the present methods. The current methods have either long reaction times, or have forced conditions. Moreover, our protocol is also suitable for multimolar preparations.

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