chemistry proceedings

MDPI

Proceeding Paper

Synthesis and Reactivity of 2-Acetylthiophenes Derivatives †

Hadjer Missoum [1],*, Yazid Datoussaid [1,2], Noureddine Choukchou-braham [1], Julio A. Seijas [3] and M. Pilar Vázquez-Tato [3]

[1] Laboratoire de Catalyse et Synthèse en Chimie Organique, Faculté des Sciences, Université de Tlemcen, BP 119, Tlemcen 13000, Algeria; email1@email.com (H.M.); email2@email.com (Y.D.); email3@email.com (N.C.-b.)
[2] Ecole Supérieure en Sciences Appliquées de Tlemcen (ESSAT), Tlemcen 13000, Algeria
[3] Departamento de QuímicaOrgánica, Facultade de Ciencias, Universidade de Santiago de Compostela, 5Campus Terra, 27080 Lugo, Spain; julioa.seijas@usc.es (J.A.S.); pilar.vazquez.tato@usc.es (M.P.V.-T.)
* Correspondence: hadjer.missoum@univ-tlemcen.dz
† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

Abstract: Thiophene is a five membered sulfur containing hetero aromatic ring. Its presence in compounds of therapeutic interest is remarkable, leading to various research to develop strategies to synthesize new biologically active thiophene analogues. 2-acetylthiophenes derivatives; and due to the presence of the ketone fonction are a good intermediates to prepare important compounds. Since its discovery, the Vilsmeier-Haack reaction has always been a subject of great interest to organic chemists and continues to attract considerable attention. It is a powerful tool in organic chemistry. This reagent is widely used for chloroformylation of ketones giving β-chloroacroleïnes ; scaffolds to prepare 5-aryl-2-acetylthiophenes derivatives. Our team aims to develop and functionalize heterocyclic compounds with promising biological and pharmacological activities including some new concept of green chemistry; as a part of our research, different derivatives of 5-aryl-2-acetylthiophenes were achieved in good yields that are used then to prepare new compounds.

Keywords: Heterocycle; thiophene; Vilsmeier-Haack; β-chloroacroleïnes; biologically active thiophene

Citation: Missoum, H.; Datoussaid, Y.; Choukchou-braham, N.; Seijas, J.A.; Vázquez-Tato, M.P. Synthesis and Reactivity of 2-Acetylthiophenes Derivatives. *Chem. Proc.* **2023**, *14*, x. https://doi.org/10.3390/xxxxx

Academic Editor(s): Name

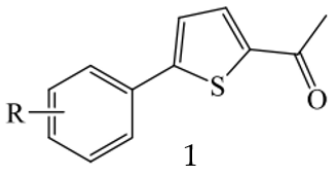
Published: 15 November 2023

1. Introduction

Highly substituted thiophenes form an internal part of numerous natural products and pharmaceuticals [1]; among the biological activities described in litterature: anti- tumor [2], anti-inflammatory, anti-Alzheimer, antiviral, etc. [3].

Thiophenes derivatives are prepared through several methodes, for 5-aryl-2-acetylthiophenes derivatives we start by the preparation of β-chloroacroleïnes via Vilsmeier-Haack reaction followed by a cyclisation to reach our target molecules.

The research teams of our laboratory focus their efforts on the synthesis of new heterocyclic compounds with promising biological and pharmacological activities via modern and ecofriendly strategies [4–8]. As a part of our work, different derivatives of 5-aryl-2-acetylthiophenes (1) were achieved in good yields that are then used to prepare new compounds (Figure 1).

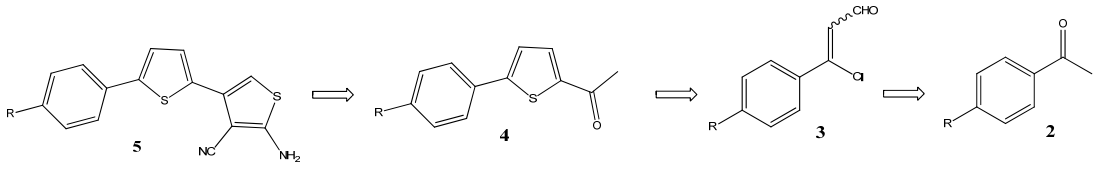


1

Figure 1. 5-aryl-2-acetylthiophenes derivatives.

2. Results and Discussion

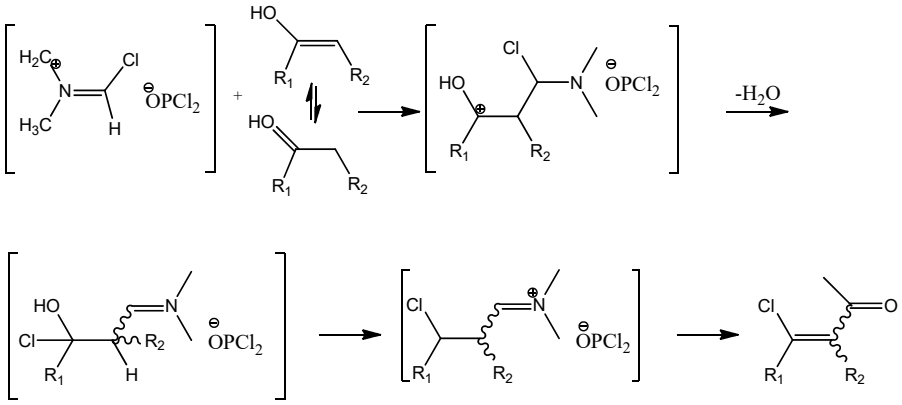
In this communication, the retrosynthetic scheme that has been propounded is the following (Scheme 1).



Scheme 1. Retrosynthetic scheme of the synthesis of 5-aryl-2-acetylthiophenes derivatives.

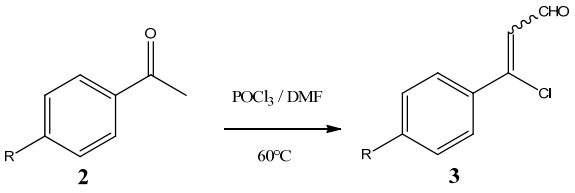
The Vilsmeier-Haack reagent is used in several reactions; formylation [9], chlorination [10], chloroformylation [11], aromatization [12], cyclization [13] … etc. In the presente work we focus on the chloroformylation of acetophenones derivatives to prepare β-aryl-β-chloroacroleïne followed by a cyclisation to obtain the corresponding thiopenes.

The Vilsmeier-Haack reagent is an iminium salt prepared by reacting phosphorus oxychloride ($POCl_3$) and DMF at 0 °C. The chloromethyleneiminium salt interacts with the enolic form of acetophenone to form an iminium salt which is rapidly hydrolyzed to isolate β-chloroacroleins (Scheme 2).



Scheme 2. Synthesis of chloromethyleneiminium salt.

Different acetophenone derivatives (2) were used to prepare β-aryl-β-chloroacroleïne (3) with good yields (Scheme 3).

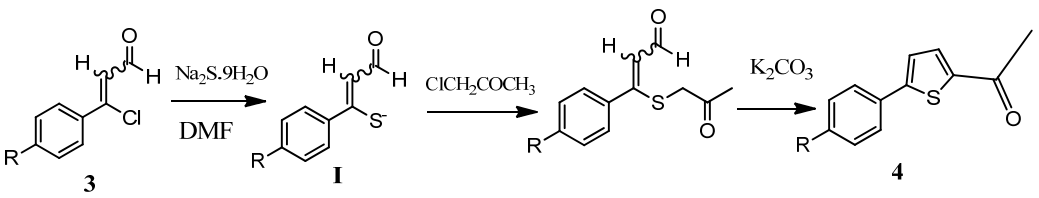


R= OMe, F, Cl, Me , NO_2

R :OMe Yield :61%
R :F Yield :69%
R Cl Yield :63%
R :Me Yield :87%
R :OMe Yield :61%
R :NO_2 Yield :85%

Scheme 3. Syhthesis of β-aryl-β-chloroacroleïne.

The obtained intermediates (3) react with sodium sulfide nonahydrated to form thiolate (I) as intermediate, chloroacetone is added followed by potassium carbonate to give 5-aryl-2-acetylthiophenes derivatives (4) in good yields (Scheme 4).



Scheme 4. Reaction pathway of 5-aryl-2-acetylthiophenes derivatives.

The structures of all products were confirmed by ^{1}H NMR spectrum. The spectrum (Figure 2) of 1-(5-(4-methoxyphenyl)thiophen-2-yl)ethanone (R:OMe) shows the disappearance of the aldehyde (O=C-**H**) pic around 10.18–10.25 ppm of the 3-chloro-3-(4-méthoxyphényl) acrylaldéhyde and of course the presence of a singlet peak at 2.55 ppm corresponding to the protons (O=C-C**H**$_3$), in addition to the 2 protons of the thiophene ring at 7.63–7.47 ppm.

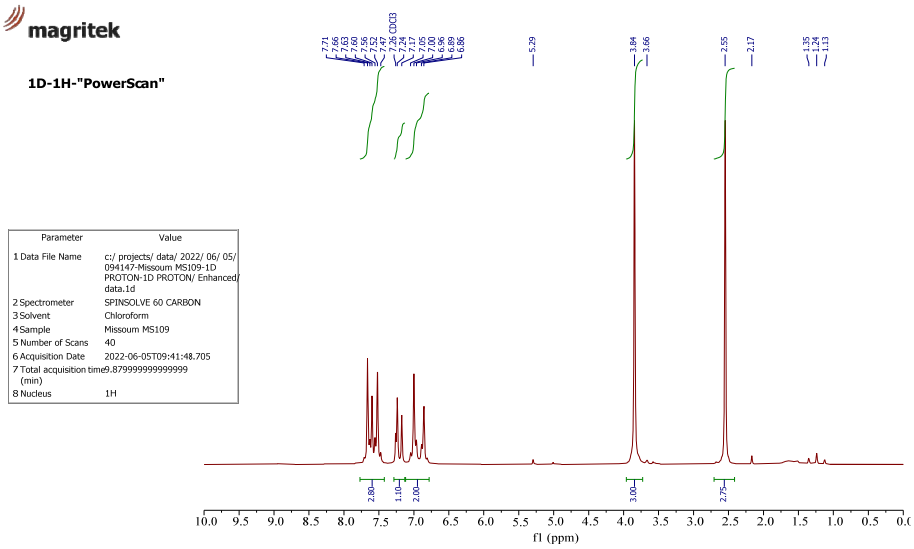
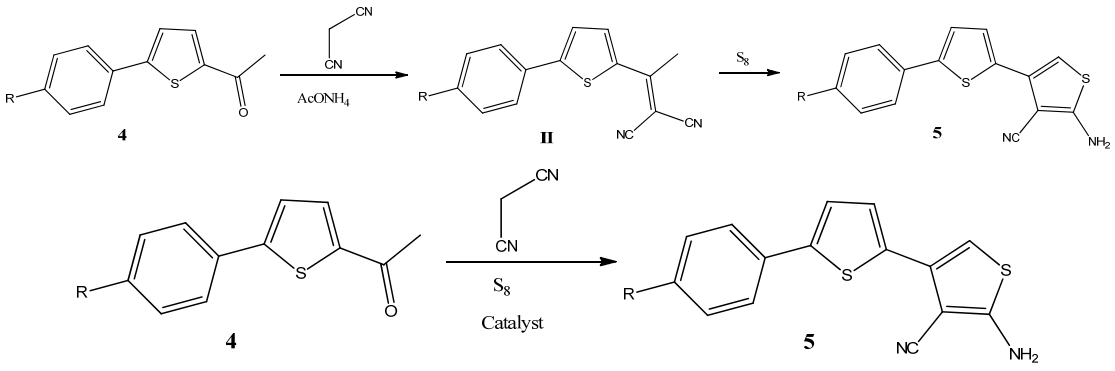


Figure 2. ^{1}H-NMR spectrum of 1-(5-(4-methoxyphenyl)thiophen-2-yl)ethanone.

The presence of the ketone in the molecule (4) offers a multitude interesting reactions such as the preparation of a second thiophene ring (5). Two suggestions are made (Scheme 5):

(1) Preparation of the corresponding alkene by a Knoevenagel condensation (II) followed by a Gewald reaction (5).
(2) One pot reaction using a catalyst.



Scheme 5. Synthesis of the second thiophene ring using two methods.

Reaction between 1-(5-(4-methoxyphenyl)thiophen-2-yl)ethanone and malononitrile in the presence of ammonium acetate was carried out ; as the carbon chain gets bigger, Knoevenagel reaction becomes more difficult which requires more than 72 to reach the new product with low yield, an alternative way is under study to pick up the right catalyst for those type of reactions.

General experimental procedure:

(1) Synthesis of β-aryl-β-chloroacroleïne:

At 0 °C, 1.5 eq of $POCl_3$ was slowly added to 1.5 eq of DMF and the mixture was stirred for 10 min. Once the salt is ready, (0.7 g) of acetophenones (5) in DMF was added dropwise with stirring. The reaction mixture was heated at 60 °C. The evolution of the reaction was followed by TLC, after the completion of the reaction, the solution was cooled at room temperature then poured slowly into a sodium acetate aqueous solution (10%) pH = 4. The solid obtained was filtered and washed with water to afford β-aryl-β-chloroacroleïne, which were used in the next step without further purification. For analysis a small amount of the obtained solid was recrystallized from cyclohexane.

(2) Synthesis of 5-aryl-2-acetylthiophenes derivatives:

To a solution of 1 eq of Na_2S9H_2 in DMF was added β-aryl-β-chloroacroleïne previously prepared. The mixture was stirred at 60 °C, The evolution of the reaction was followed by TLC, after the completion of the reaction, 1 eq of Chloroacetone was rapidly added and the reaction was stirred during 6 h at 60 °C. 1 eq of K_2CO_3 dissolved in 1 mL of water was added to the reaction. The mixture was stirred during 30 min at 60 °C, cooled at room temperature and poured in water. The solid obtained was filtered and the crude product was washed with water and recrystallized from ethanol.

3. Conclusions

In the present communication, we have talked about the synthesis of 5-aryl-2-acetylthiophene derivatives (4). Coming works will be on the preparation of a second thiophene ring using a simple and effective way.

References

1. Tümer, F.; Ekinci, D.; Zilbeyaz, K.; Demir, Ü. An efficient synthesis of substituted 4-Aryl-3-Cyano-2-Amino thiophenes by a stepwise Gewald Reaction. *Turk. J. Chem.* **2004**, *28*, 395–404.
2. Puterová, Z; Krutošíková; A; Vegh, D. Gewald reaction: Synthesis, properties and applications of substituted 2-aminothiophenes. *Arkivoc* **2010**, *1*, 209–246.
3. Wang, Z., Kang, D., Chen, M., Wu, G., Feng, D., Zhao, T., Zhou, Z., Huo, Z., Jing, L., Zuo, X.; et al. Design, synthesis, and antiviral evaluation of novel hydrazone-substituted thiophene [3, 2-d] pyrimidine derivatives as potent human immunodeficiency virus-1 inhibitors. *Chem. Biol. Drug Des.* **2018**, *92*, 2009–2021.
4. Yazid, D.; Tewfik, A.D.; Nawel, M.; Brahmi, L.; Zahira, K.; Rachida, H.; Noureddine, C.B. Ecofriendly synthesis of formamidine derivatives catalyzed by Al-MCM-41 Mesoporous materials. *Lett. Org. Chem.* **2022**, *19*, 347–352.
5. Belhadj, F.; Kibou, Z.; Cheikh, N.; Choukchou-Braham, N.; Villemin, D. Convenient access to new 4-substituted aminopyrido [2, 3-d] pyrimidine derivatives. *Tetrahedron Lett.* **2015**, *56*, 5999–6002.
6. Mehiaoui, N.; Kibou, Z.; Gallavardin, T.; Leleu, S.; Franck, X.; Mendes, R.F.; Paz, F.A.A.; Silva, A.M.; Choukchou-Braham, N. Novel bis-(3-cyano-2-pyridones) derivatives: Synthesis and fluorescent properties. *Res. Chem. Intermed.* **2021**, *47*, 1331–1348.
7. Nouali, F.; Kibou, Z.; Boukoussa, B.; Choukchou-Braham, N.; Bengueddach, A.; Villemin, D.; Hamacha, R. Efficient multicomponent synthesis of 2-aminopyridines catalysed by basic mesoporous materials. *Res. Chem. Intermed*. **2020**, *46*, 3179–3191.
8. Kibou, Z.; Villemin, D.; Lohier, J.F.; Cheikh, N.; Bar, N.; Choukchou-Braham, N. Easy solventless synthesis of new mono and bis amino-5H-chromeno [3, 4-c] pyridin-5-one derivatives. *Tetrahedron* **2016**, *72*, 1653–1661.
9. Popov, A.V.; Kobelevskaya, V.A.; Larina, L.I.; Rozentsveig, I.B. Synthesis of poly-functionalized pyrazoles under Vilsmeier-Haack reaction conditions. *Org. Chem.* **2019**, 1–14.
10. Jass, P.A.; Rosso, V.W.; Racha, S.; Soundararajan, N.; Venit, J.J.; Rusowicz, A.; Swaminathan, S.; Livshitz, J.; Delaney, E.J. Use of N-trifluoroacetyl-protected amino acid chlorides in peptide coupling reactions with virtually complete preservation of stereochemistry. *Tetrahedron* **2003**, *59*, 9019–9029.
11. Meesala, R.; Nagarajan, R. Synthesis of new diheteroarylcarbazoles: A facile and simple route of 3, 6-di (pyrazol-4-yl) carbazoles. *Tetrahedron Lett.* **2006**, *47*, 7557–7561.
12. Marson, C.M. *Synthesis Using Vilsmeier Reagents*; CRC Press: Boca Raton, FL, USA, 2018.

13. Liu, C.; Hu, J.; Xu, H.; Lu, Z.; Yu, X.; Lin, Z. Synthesis, Characterization, and Crystal Structure of a Phenanthroindolizine Skeleton from 18-Acetamino-7-Oxo-Dehydroabietane by Vilsmeier-Haack Reaction. *Chem. Nat. Compd.* **2015**, *51*, 306–310.