[a006]

AN EASY SYNTHESIS OF 5-NITRO-THIOPHENES AND 3-AMINO-2-NITRO-THIOPHENES

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Abstract

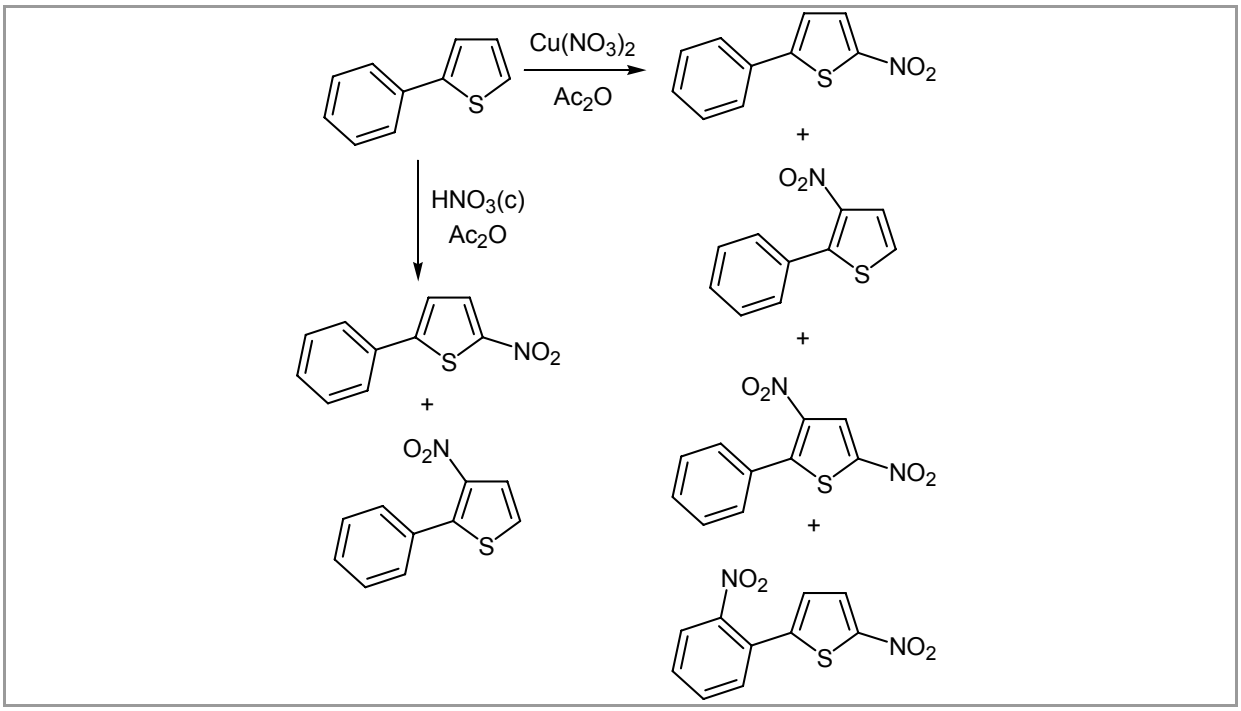
A one-step preparation of substituted 5-nitro thiophenes and 3-amino-2-nitrothiophenes starting from corresponding β-chloroacroleins and β-chloropropenonitriles was developed. Sodium sulfide, bromonitromethane and sodium hydroxide were used as reagents to obtain the expected compounds in good yields with a simple and easy work up procedure.

1. Introduction :

Nitrothiophenes have some versatile biological uses. They inhibit the growth of *E.Coli*, *M. Luteus* and *A. Niger* [1] and are used as precursors of N-(5-substituted) thiophene-2-alkylsulfonamides which are potent inhibitors of 5-lipoxygenase.[2] Moreover, 3-amino-2-nitrobenzo[*b*]thiophenes were used as starting material for the preparation of the corresponding dye.[3]

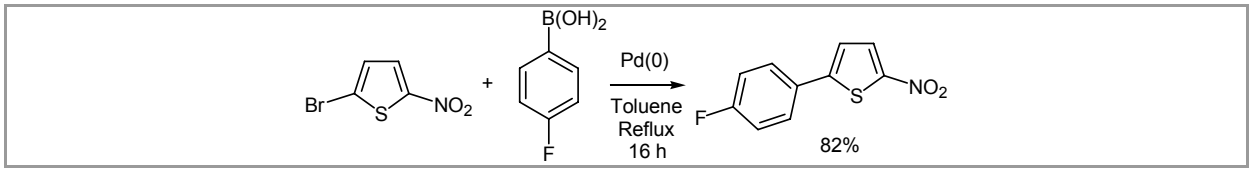
5-Phenyl 2-nitrothiophene has been prepared by direct nitration of the 2-phenyl thiophene with either nitric acid or different proportions of $Cu(NO_3)_2$ in acetic anhydride[4] but in all cases mononitration was not selective and also dinitration took place. When nitric acid was employed, a mixture of 2-nitro-5-phenyl and 3-nitro-2-phenyl thiophenes was obtained. If the reaction was carried out with $Cu(NO_3)_2$, mixtures of 3-nitro-2-phenyl, 2-nitro-5-phenyl, 3,5-dinitro-2-phenyl and 2-nitro-5-(2-nitrophenyl) thiophenes was recovered as final products (scheme 1).

1. Morley, J. O.; Matthews, T. P. *Org. Biomol. Chem.* **2006**, *4,* 359.
2. Beers, S. A.; Malloy, E. A.; Wu, W.; Wachter, M.; Ansell, J.; Singer, M.; Steber, M.; Barbone, A.; Kirchner, T.; Ritchie, D.; Argentieri, D. *Bioorg. Med. Chem.* **1997**, *5*; 779.
3. Hallas, G.; Towns, A. D. *Dyes and Pigments.* **1997**, 3, 219.
4 (a)Gronowitz, S.; Gjos, N. *Acta Chem. Scand*. **1967**, *21*, 2823-2831. (b) Gronowitz, S.; Gjos, N. *Acta Chem. Scand*. **1972**, *26*, 1851-1855.



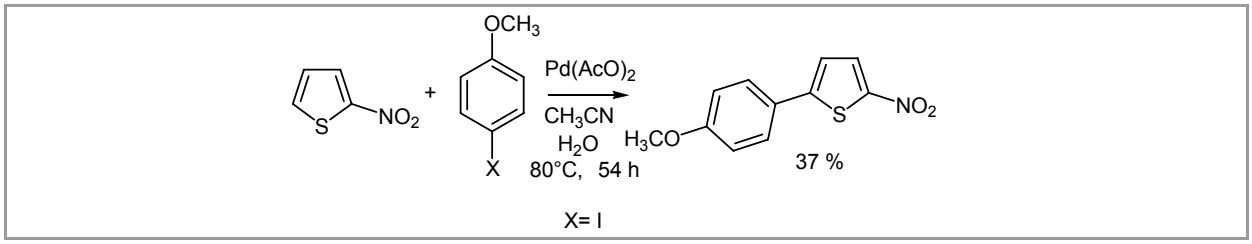
Scheme 1 Directly nitration of 2-phenyl thiophene by either concentrated nitric acid or copper nitrate in acetic anhydride.

Another way for preparing 2-aryl-5-nitrothiophenes is the Suzuki coupling of the 2-bromo-5-nitrothiophene with the corresponding aryl boronic acids (scheme 2). **¡Error! No se encuentra el origen de la referencia.**



Scheme 2 Synthesis of the 5-(4-fluoro phenyl)-2-nitrothiophene by Suzuki coupling (palladium complexes were used).

This coupling reaction was applied for the same purpose in order to obtain the 2-nitro-5-(4-methoxy) phenyl thiophene from the corresponding iodophenyl derivative (scheme 3).[4,5] Even if Suzuki coupling allows to obtain the aryl nitrothiophene in good yield (scheme 2), usually palladium catalysis requires long reaction time to prepare the targeted derivatives (schemes 2 and 3). In the case where p-iodoanisole was employed (scheme 3), isolated yield was low.[5]



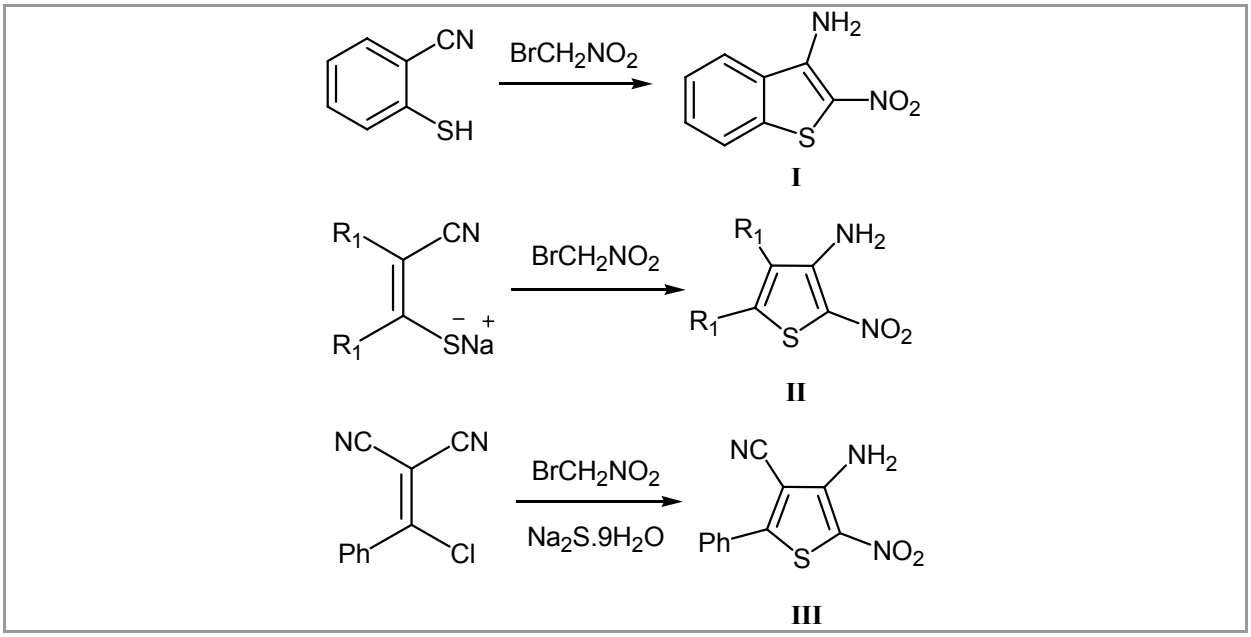
Scheme 3 Synthesis of the 5-(4-methoxy phenyl)-2-nitro thiophene by Suzuki coupling (palladium acetate was used).

On the other hand, 3-amino-2-nitrothiophenes were not very much described using bromonitromethane as reagent. Only a few teams worked in this field of investigation.

5. Gozzi, C.; Lavenot, L.; llg, K.; Penalva, V.; Lemaire, M. *Tetrahedron Letters,* **1997**, *38*, 8867-8870.

Fishwick *et al.* described the preparation of 3-amino-2-nitrobenzo[b]thiophene (**I**) starting from 2-sulfanylbenzonitrile and bromonitromethane.[6] In the same paper, they synthesized some 3-amino-2-nitrothiophenes starting from sodium salt of disubstituted 3-sulfanyl-2-propenenitriles and bromonitromethane.[6] They obtained compounds (**II**) in yields ranging from 30% to 70%.

Only one thiophene (**III**) was synthesized by Gewald *et al*., starting from a α,βdisubstituted β-chloropropenonitrile and using sodium sulfide and bromonitromethane (Scheme 4).[7]



Scheme 4. 3-Amino-2-nitrophene in literature. R_1= -S-Me, R_2= -CN, -CO_2Et, -$CONH_2$; R_1= -NH-Ph, R_2= -CN, -CO_2Et, -SO_2PH.

Bromonitromethane is a versatile reagent used in stabilized solutions as biocide,[8] in the synthesis of 1-bromo-1-nitroalkan-2-ols,[9] polyfunctionalized nitrocyclopropanes,[10] aryl nitromethanes and as bromine donor.[11] It has also been utilized in the synthesis of 2-nitrobenzofuran and 2-nitro-2,3-dihydrobenzofuran-3-ols[12,13], nitro benzothiophenes and nitrothiazoles.[6]

In the thiophene series only few examples have been described; in the case of 2-*tert* butyl-5-nitro thiophene[11], no experimental details are given (Scheme 5).

As a continuation of previous research on the synthesis of functionalized thiophenes and their use for the preparation of condensed systems (Scheme 5)[14,15,16] we describe the preparation of new substituted 2-aryl-5-nitro thiophenes and substituted 3-amino-2-nitrothiophenes in a one-pot procedure allowing access to the thiophene derivatives in good yields with a simple work up (scheme 6).

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6. Fishwick, B. R.; Rowles, D. K.; Stirling, C. J. M. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 1171.
7. Gewald, K.; Hain, U. *Monatsh. Chem.* 1992, 123, 5, 455.
8. Termine, E. J.; Dallmier, A. W.; Yeoman, A. M. US Patent 5,866,511.
9. Concellón, J. M.; Rodríguez-Solla, H.; Concellón, C.; García-Granda, S.; Díaz, M. R. *Org. Lett* **2006**, *8*, 5979-5982.
10. Ballini, R.; Fiorini, D.; Palmieri, A. *Synlett* **2003**, 1704-1706.
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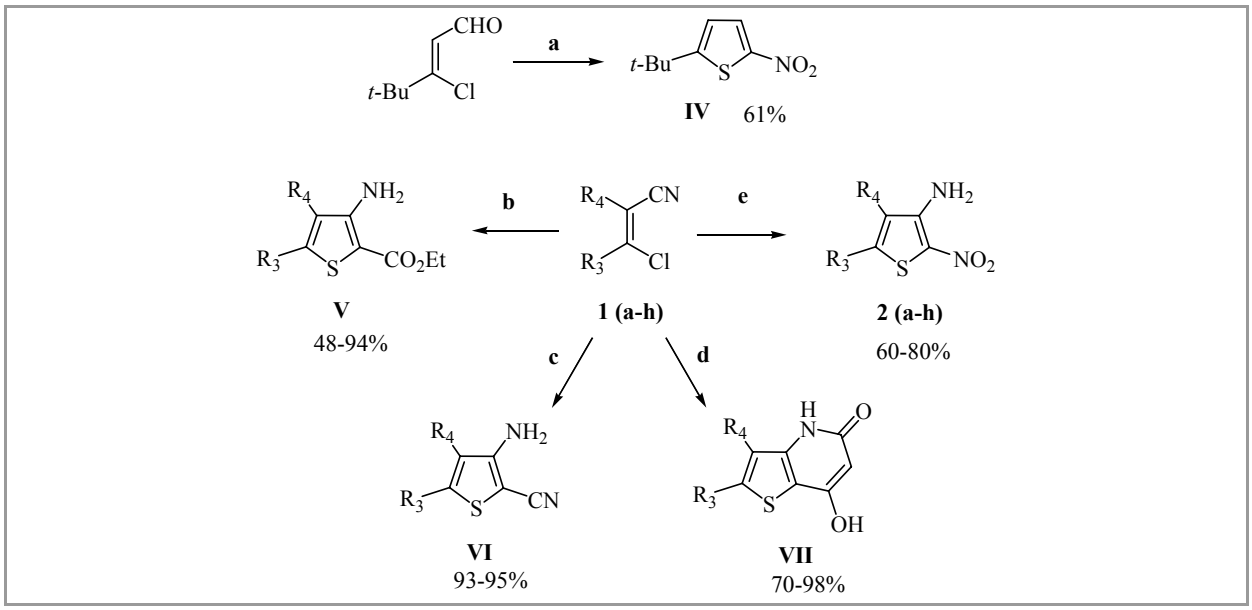
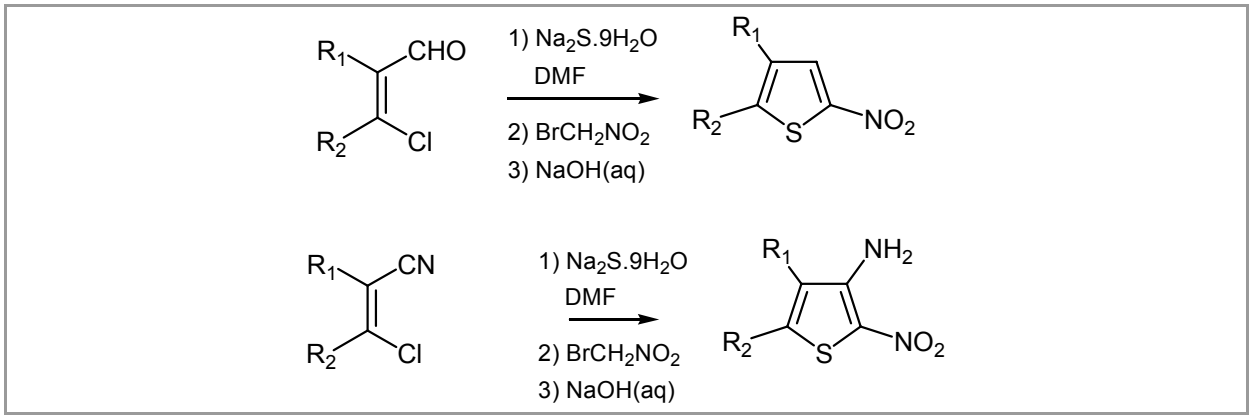
13. Tromelin, A.; Demerseman, P.; Royer, R. *Synthesis*. **1985**, *11*, 1074-1076.
14. Migianu, E.; Kirsch, G. *Synthesis* **2002**, 1096.
15. Thomae, D.; Kirsch, G.; Seck, P. *Synthesis* **2007**, 1027.
16. Thomae, D.; Kirsch, G.; Seck, P. *Synthesis* **2007**, 2153.



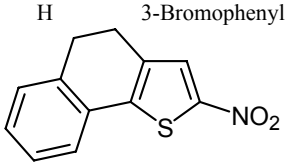
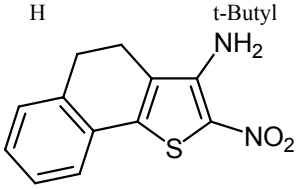
Scheme 5.Thiophenes synthezised by our laboratory. **a** $Na_2S.9H_2O$, $BrCH_2NO_2$, NaOH; **b** $HSCH_2CO_2Et$, K_2CO_3; **c** $Na_2S.9H_2O$, $ClCH_2CN$, EtONa; **d** $Na_2S.9H_2O$, $ClCH_2COCH_2CO_2Et$, EtONa; **e** $Na_2S.9H_2O$, $BrCH_2NO_2$, NaOH



Scheme 6. Developed procedure to obtain 2-aryl-5-nitro thiophenes and substituted 3-amino-2-nitrothiophenes.

Structures of prepared compounds are referred in Table 1.

Table 1. Prepared compounds.

No.	R_1	R_2	Yield (%)	No.	R_1	R_2	Yield (%)
1	H	4-Chlorophenyl	71	**9**	H	4-Methylphenyl	60
2	H	4-Fluorophenyl	61	**10**	H	4-Methoxyphenyl	62
3	H	4-Methylphenyl	82	**11**	H	4-Chlorophenyl	64
4	H	4-Methoxyphenyl	73	**12**	H	4-Fluorophenyl	80
5	H	4-Nitrophenyl	74	**13**	H	4-Nitrophenyl	70
6	H	1,1'-Biphenyl-4-yl	61	**14**	H	1,1'-Biphenyl-4-yl	78
7	H	3-Bromophenyl	70	**15**	H	t-Butyl	70
8			85	**16**			80

Acknowledgments

We are grateful of the French Ministry of National Education, Higher Education and Research for a PhD grant (D.T). We also thank to the Ministère de la Culture, de l'Enseignement Supérieur et de la Recherche de Luxembourg for the financial support.