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# Nitration of methyl-3-hydroxy- and 5-methyl-3-hydroxy-thiophene-2-carboxylate, and some chemistry of the products

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The nitration of methyl-3-hydroxythiophene-2-carboxylate furnishes two products, the lower melting of which was previously thought to be the 4- (**3**) and the other the 5-isomer (**2**); these assignments have been reversed on the basis of carbon-13 NMR. data and the revised structures have been confirmed both by *O* to *N* acyl migrations and by the preparation of the first examples (**20**) and (**23**) of the thieno[3,4-*b*][1,4]oxazine ring system from derivatives of the 4-nitro isomer.

**Keywords:** methyl-3-hydroxythiophene-2-carboxylate, nitration

Treatment of methyl 3-hydroxythiophene-2-carboxylate (**1**) with fuming nitric acid – sulfuric acid at –10°C to 0°C yields two products, one (m.p. 89–90°C) described in the literatiure[1] as the 4- (**3**), and the other (m.p. 110–111°C) as the 5-nitro derivative (**2**). These assignments have been reversed on the basis of carbon-13 NMR data and through some of their reactions. Whereas (**2**) and its derivatives behaved unexceptionally compound (**3**) underwent transformations which pointed to the existence of adjacent OH and $NO_2$ functions (see Scheme). Acylation of (**3**) gave (**11a**) andf (**11b**) and reduction of these produced the iron complexes (**12a**) and (**12b**) which yielded products in which an *O* to *N* acyl migration had occurred. In contrast, reduction of the acyl derivatives of (**2**) proceeded normally. This difference in behaviour of the acyl compounds afforded methods for the preparation of substances derived from (**2**) and (**3**) without the necessity of isolating the two isomers from the nitration of (**1**). The most convenient procedure involved the acidification of the reaction mixture from the reduction and extraction of the amide (**13a**) into ether; the *O*-acyl amino compound (**9**) produced from the acyl derivative of (**2**) remained in the acidic aqueous layer and was isolated by basification. The ratio of (**9a**) to (**13a**) was about 3:2.

Further evidence for the structure of (**3**) was provided by the construction of a ring at the 3- and 4-positions of its thiophene system. Alkylation of (**3**) with ethyl bromoacetate and potassium cabonate in DMSO gave the diester (**19**); this on reduction with iron and acetic acid yielded the spontaneously cyclised product (**20**). Reduction of (**19**) in the presence of acetic anhydride trapped the intermediate amine as its acetyl derivative (**22a**), which, on treatment with sodium hydride in DMSO followed by aqueous workup gave the acid (**22c**) instead of the expected cyclised product (**23**). It was thought that cyclisation had indeed occurred but the product had hydrolysed during the workup. This was confirmed when (**22c**) was cyclised to (**23**) in acetic anhydride under reflux followed by a nonaqueous workup; the product was rapidly hydrolysed to (**22c**) on treatment with water. No other examples of the thieno[3,4-*b*][1,4]-oxazine ring system present in (**20**) and (**23**) were found in the literature.

In order to avoid the problem of isomer separation nitration of methyl 5-methyl-3-hydroxythiophene-2-carboxylate (**24**) was attempted but only an *O*-nitro compound was obtained. However the *O*-acetyl derivative (**26**) of (**24**) was nitrated successfully and reduction of the product (**28**), as before, was accompanied by *O*- to *N*-acyl migration giving the 5-methyl homologue (**29**) of (**13a**).

Carbon-13 NMR substituent shift values have been calculated for 2- and 3-$NO_2$, 2- and 3-$NH_2$, 2- and 3-NHAc, 3-$OCH_2CO_2Et$ and 3-OMe groups from compounds prepared in this work and from a wide range of appropriate thiophene spectra recorded in the literature.

Table 1 Comparison of carbon-13 NMR data for alternative structures

Table 2A: C-13 NMR. spectra of compounds derived from methyl-3-hydroxy-5-nitrothiophene-2-carboxylate

Table 2B: C-13 NMR spectra of compounds derived from methyl-3-hydroxy-4-nitrothiophene-2-carboxylate (in $CDCl_3$)

Table 3: Carbon-13 NMR substituent shifts for thiophene obtained from the present work and from the database of literature values.

Four Schemes.

**SAFETY NOTE:** Mixtures of fuming nitric acid and acetic anhydride are known to be dangerously unstable and can detonate (*Brethericks Handbook of Reactive Chemical Hazards*, 6th edn, ed. P.G. Urben, Vol. 1, 1568, Butterworth Heinemann, Oxford 1999; see also G.A. Olah, *Chem. Brit*., August 1996, **32**, 21). in the present case the acid used is not fuming. **BUT CAUTION IS ADVISED**.

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## Reference cited in this synopsis

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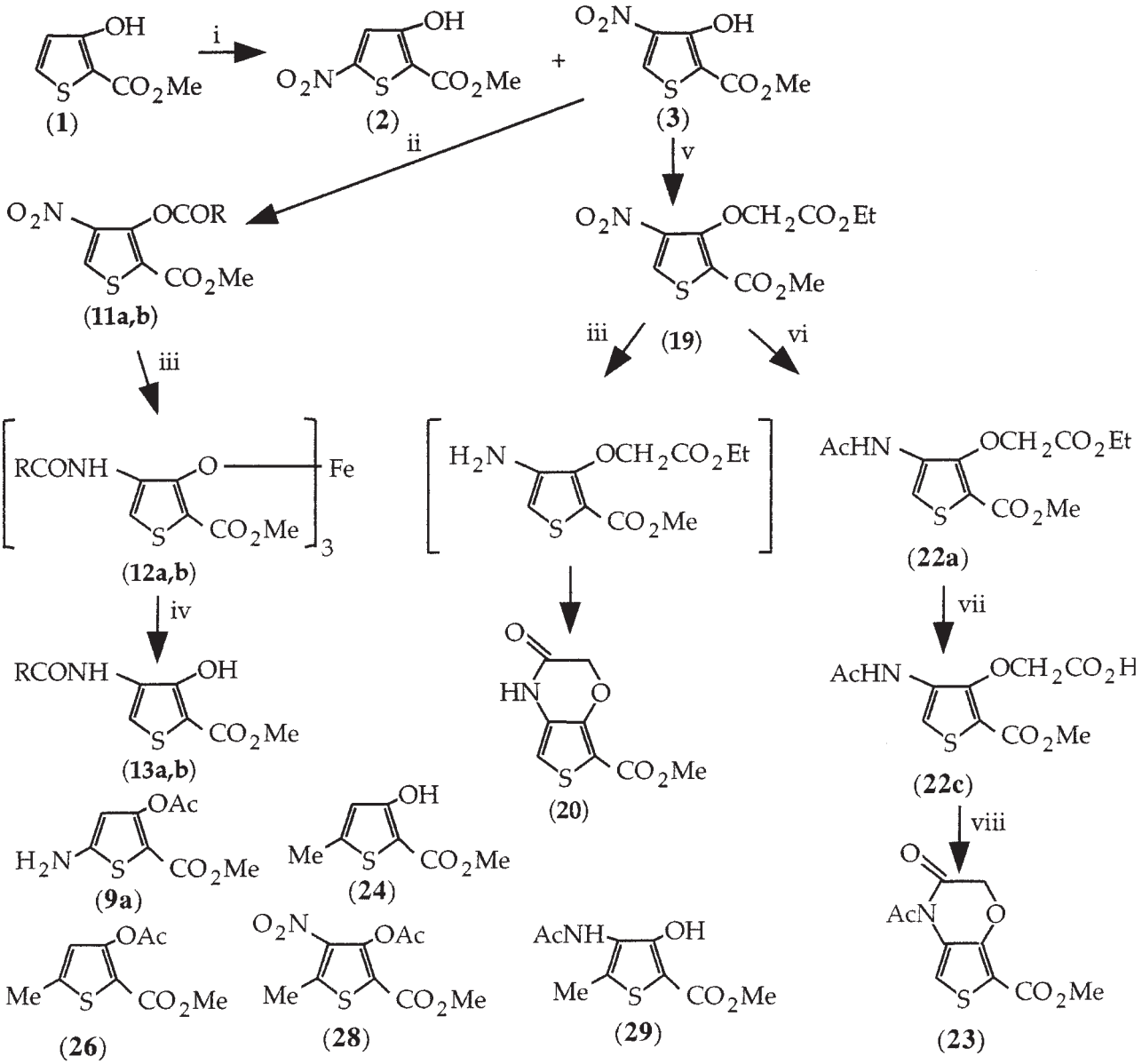


**Scheme 1** a, R = Me; b, R = OEt
i $HN)_3$-$H_2SO_4$; ii $Ac_2O$-(for 11a) $ClCO_2Et$- (for 11b) $C_5H_5N$; iii Fe-AcOH;
iv HCl-aq; v$BrCH_2CO_2Et$-$K_2CO_3$-DMSO; vi Fe-AcOH-$Ac_2O$; vii NaH-DMSO; viii $Ac_2O$