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Fluorination and chlorination of nitroalkyl groups

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Abstract—Heterocycles substituted with a nitromethyl (CH_2NO_2) or phenyl-nitromethyl ($CHPhNO_2$) group were prepared by reaction of a methyl- or phenylmethyl-substituted heterocycle, respectively, with lithium di-isopropylamide followed by quenching the intermediate carbanion with methyl nitrate. Conversion of CH_2NO_2 attached to an alkyl or aryl moiety into a dichloronitromethyl (CCl_2NO_2) group was achieved using *N*-chlorosuccinimide and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane. Similarly, CH_2NO_2 attached to an alkyl or aryl group was converted into difluoronitromethyl (CF_2NO_2) using either 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™) or *N*-fluorobenzenesulfonimide with DBU as base and dichloromethane as solvent. Reaction of ω-nitroacetophenone with Selectfluor/DBU in dimethylformamide followed by acidification and distillation gave the parent difluoronitromethane in a useful 'one-pot' procedure.

1. Introduction

Difluoromethylornithine (Eflornithine, DFMO, Fig. 1) is an important drug for treating trypanosomiasis (African sleeping sickness) that acts as a suicide inhibitor of ornithine decarboxylase.[1] We wished to develop a synthesis of this compound which avoids the use of the Freon (chlorodifluoromethane) that is used in the current synthesis.[2] It was desirable to generate the difluoromethyl group of DFMO using relatively non-toxic and inexpensive sources of the fluorine atoms. To this end we conceived of the difluoronitromethyl group (CF_2NO_2) as a possible precursor of the CF_2H group. In this paper we describe methods for accessing compounds containing the CF_2NO_2 group linked to alkyl, aryl and heteroaryl substituents by electrophilic fluorination of the nitromethyl (CH_2NO_2) group via the corresponding nitro-stabilised carbanion. The achievement of this goal required that methods for preparing the precursor nitro compounds were improved. During this work we also developed an efficient synthesis of the parent molecule CHF_2NO_2, as well as syntheses of compounds containing $CHFNO_2$ and CCl_2NO_2 groups. We have utilised the commercially available 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]-octane bis(tetrafluoroborate) (Selectfluor™, abbreviated Selectfluor) and *N*-fluorobenzenesulfonimide as fluorinating agents and *N*-chlorosuccinimide for chlorinations. Peng and Shreeve described fluorinations of nitro compounds using Selectfluor that lead mainly to monofluoro products.[3] Recently, α-nitro esters were converted into monofluoro derivatives using Selectfluor in the presence of a cinchona alkaloid that led to an excess of one enantiomer.[4] Previously, nitro compounds (e.g., nitrocyclopentane) had been converted into monofluoro derivatives using sodium hydride or methoxide with acetyl hypofluorite.[5,6] The reaction conditions employed in the present work ensured good yields of difluoro-products. Some examples of the preferred methodology were reported in a preliminary communication, as well as the finding that fluorinations with Selectfluor can alternatively be performed under sonochemical conditions giving high yields of the desired CF_2NO_2 products.[7]

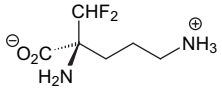

Figure 1. Structure of difluoromethylornithine.

2. Results and discussion

2.1. Synthesis of precursor nitro compounds

Simple primary and secondary nitroalkanes have been synthesised by reaction of an alkyl halide with silver nitrite or

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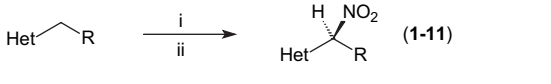
sodium nitrite in dimethylformamide (DMF).[8] However, these reactions give nitrite esters and other by-products, although recently it was claimed that improved yields of the nitro compound are obtained under aqueous conditions.[9] Although the classical methodology was acceptable for preparing some of the nitro compounds described in this paper, we needed to develop conditions for the reliable synthesis of nitrophenylmethyl- (**1** and **2**) and nitromethyl- (**3**–**11**) heterocycles. This method involved treatment of either a phenylmethyl (leading to **1** and **2**) or methyl-substituted precursor (leading to **3**–**11**) with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) followed by addition of methyl nitrate (Scheme 1). The success of this reaction benefits from the use of tetrahydrofuran (THF) as solvent and enables products to be readily obtained in a one-pot reaction. Previously, Feuer and Lawrence reported the nitration of methyl groups of heterocycles by treatment with sodium amide in liquid NH_3 followed by addition of propyl nitrate.[10] However, these conditions are less safe and convenient than the method reported herein.

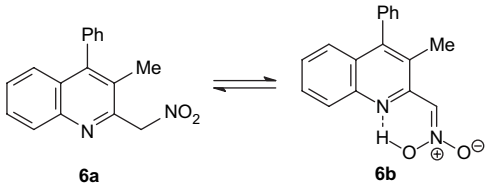


1 R = Ph, Het = 2-pyridyl
2 R = Ph, Het = 4-pyridyl
3 R = H, Het = 2-pyridyl
4 R = H, Het = 4-pyridyl
5 R = H, Het = 2-quinolyl
6 R = H, Het = 3-methyl-4-phenyl-2-quinolyl
7 R = H, Het = 4-chloro-2-quinolyl
8 R = H, Het = 4-quinolyl
9 R = H, Het = 6-phenanthryl
10 R = H, Het = 2-benzothiazolyl
11 R = H, Het = 2-benzoxazolyl

Scheme 1. Synthesis of nitroalkyl-heteroaromatic compounds (*reagents and conditions*: (i) LDA in THF, −40 °C; (ii) $MeONO_2$).

The products were characterised primarily by ^1H and ^{13}C NMR spectroscopy. These techniques showed that compounds **1** and **2**, and the nitromethylbenzoxazole **11** existed entirely as their *aci*-tautomer, whilst all the other nitromethyl compounds were a mixture of both forms (Scheme 2). Thus, NMR data showed that 4-phenyl-3-methyl-2-nitromethylquinoline **6a** exists in equilibrium with **6b** (Scheme 3). The ^1H NMR spectrum showed the signal for the vinyl proton in **6b** at δ 6.2 ppm and the signal for the NH proton at 13.5 ppm.

Scheme 2. Tautomerism of nitro compounds (see Section 4 for proportions of A and B forms).

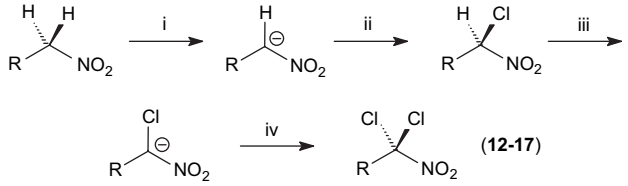


Scheme 3. Tautomeric equilibrium with **6a**/**6b**.

The ratios between the tautomers were calculated from NMR data and are given in Section 4.

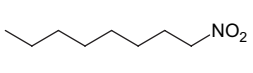
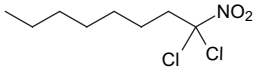
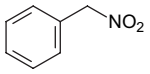
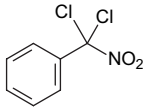
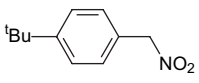
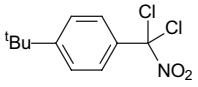
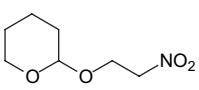
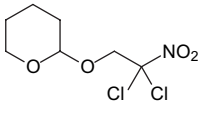
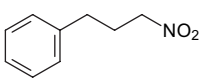
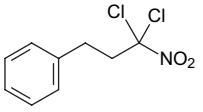
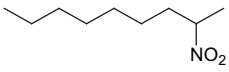
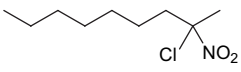
2.2. Chlorination of nitroalkyl groups

Compounds containing the dichloronitromethyl group (CCl_2NO_2), prepared by chlorination of primary nitro compounds with sodium hypochlorite, have been used as intermediates in the synthesis of branched-chain cyano sugars.[11] We have investigated their direct synthesis from primary nitro compounds as a model for the fluorination of nitroalkanes, as required for the projected synthesis of DFMO. We have found favourable conditions for the electrophilic dichlorination of a variety of primary nitro compounds in high yields using *N*-chlorosuccinimide and a catalytic amount of DBU (10 mol %) as base and with dichloromethane (DCM) as the solvent (Scheme 4 and Table 1). However, the yield of 2-chloro-2-nitrooctane from 2-nitrooctane was low even when 1 equiv of DBU was used. A much higher yield of 2-chloro-2-nitrooctane was obtained using 1 equiv of KOH in MeOH. Ballini et al.[12] have reported dichlorination of nitro compounds using *N*-chlorosuccinimide with sodium methoxide as base.



Scheme 4. Synthesis of dichloronitro compounds (*reagents*: (i) DBU (10 mol %) in DCM; (ii) and (iv) *N*-chlorosuccinimide; (iii) DBU/succinimide anion).

Table 1. Chlorination of nitro compounds

Entry	Substrate	Product	Yield (%)
12			61
13			86
14			89
15			70
16			92
17			20,[a] 59[b]

[a] DBU (1 equiv) was used.
[b] KOH (1 equiv) in MeOH was used.