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Tetrahedron 63 (2007) 11160–11166
Tetrahedron

Fluorination and chlorination of nitroalkyl groups

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Received 29 August 2006; revised 23 July 2007; accepted 8 August 2007
Available online 14 August 2007

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]

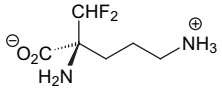

Figure 1. Structure of difluoromethylornithine.

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

Keywords: Heterocycle; Nitration; Chlorination; Fluorination; Selectfluor™; *N*-Fluorobenzenesulfonimide; Triphenyltin hydride.
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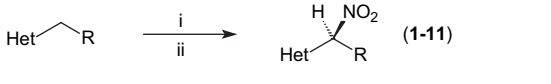
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.08.020

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.

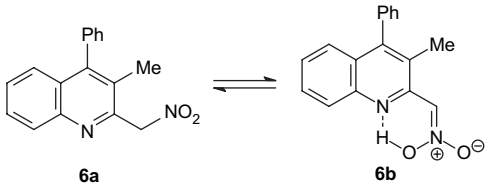


1 R = Ph, Het = 2-pyridyl
2 R = Ph, Het = 4-pyridyl
3 R = H, Het = 2-pyridyl
4 R = H, Het = 4-pyridyl
5 R = H, Het = 2-quinolyl
6 R = H, Het = 3-methyl-4-phenyl-2-quinolyl
7 R = H, Het = 4-chloro-2-quinolyl
8 R = H, Het = 4-quinolyl
9 R = H, Het = 6-phenanthryl
10 R = H, Het = 2-benzothiazolyl
11 R =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

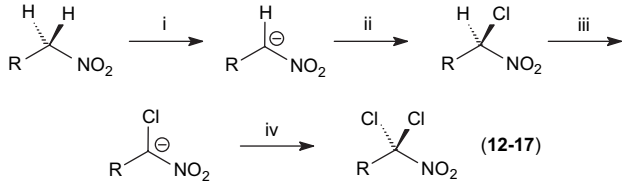


Scheme 3. Tautomeric equilibrium with **6a**/**6b**.

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

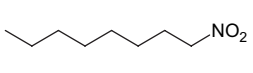
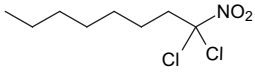
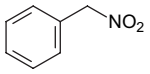
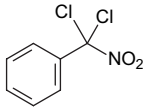
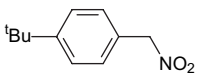
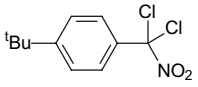
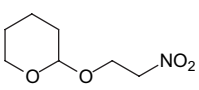
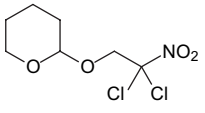
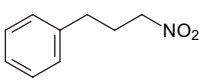
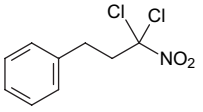
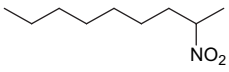
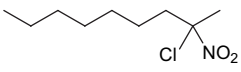
2.2. Chlorination of nitroalkyl groups

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

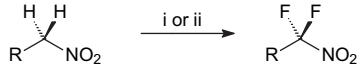
Entry	Substrate	Product	Yield (%)
12			61
13			86
14			89
15			70
16			92
17			20,[a] 59[b]

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

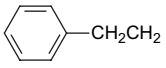
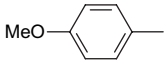
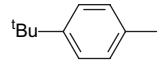
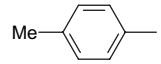
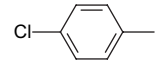
2.3. Fluorination of nitroalkyl groups

We have used the common electrophilic fluorinating agents, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor)[13,14] and *N*-fluorobenzenesulfonimide[15] for reactions with carbanions derived from nitro compounds. A variety of different bases and solvents were examined in an attempt to optimise the yield. Triethylamine was not useful as a base. Sodium hydride, which is a commonly used base in reactions involving Selectfluor,[16] gave the desired product and the monofluoronitro compound, but in relatively low yields. The same observation was made using KOH in MeOH. Using *N*-ethyldiisopropylamine as base gave negative results even after addition of a catalytic amount of tetrabutylammonium bromide (Bu_4NBr) to the reaction mixture. This experiment was based on the observation of Hammer et al.,[17] who reported increased dialkylation of ethyl nitroacetate in the presence of tetraalkylammonium salts. Adding Bu_4NBr to the reaction mixture containing DBU in DCM, again produced no increase in yield. The solvents explored were DCM, tetrahydrofuran (THF), MeCN and DMF. Surprisingly, the yields of the reactions in MeCN and DMF were lower than the corresponding reaction in DCM. Hence, DCM was chosen as the optimum solvent for mono- and di-fluorination (see examples in the preliminary communication[7] and Tables 2 and 3).

Table 2. Difluorination of nitro compounds (*reagents*: (i) $(PhSO_2)_2NF$/DBU in DCM; (ii) Selectfluor/DBU in DCM)

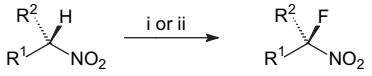


(**18-23**)

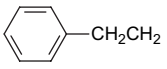
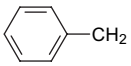
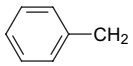
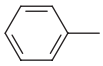
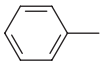
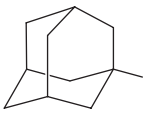
Entry	R	Yield (%)
18		41[a] 72[b]
19		80[a]
20		48[a] 68[b]
21		74[a]
22		70[a]
23	$CH_3(CH_2)_6$	50[a]

[a] Selectfluor as fluorinating agent.
[b] *N*-Fluorobenzenesulfonimide as fluorinating agent.

Table 3. Monofluorination of nitro compounds (*reagents*: (i) Selectfluor/DBU in DCM; (ii) Selectfluor/KOH in methanol)



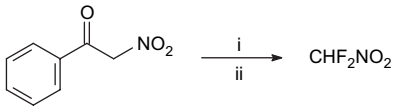
(**24-29**)

Entry	R_1	R_2	Yield (%)
24		H	90[a]
25			90[b]
26			84[a]
27		H	74[b]
28	$CH_3(CH_2)_6$	H	57[b]
29	$CH_3(CH_2)_5$	CH_3	83[b]

[a] Selectfluor/DBU in DCM.
[b] Selectfluor/KOH in methanol.

2.4. Synthesis of difluoronitromethane

The attempted fluorination of nitromethane with Selectfluor using either DBU or NaH as base in THF or Selectfluor/DBU in acetonitrile failed. Similarly, fluorination of ethyl nitroacetate with Selectfluor/DBU in acetonitrile gave only a low yield of ethyl 2-fluoro-2-nitroacetate δ 6.02 ppm (d, $^2J_{HF}$ 48.6 Hz), which was monitored by ^{1}H NMR. This compound was obtained in ca. 75% yield, accompanied by unreacted starting material, by reaction of ethyl nitroacetate with Selectfluor/NaH in THF. Monitoring the fluorination of ω-nitroacetophenone with Selectfluor/DBU in CD_3CN by ^{1}H NMR indicated conversion into ca. 50% monofluoro compound after 15 h at room temperature. After a preparative scale fluorination with Selectfluor/DBU was carried out in DMF for 40 h, initially at −10 °C and then at room temperature, water was added, and the mixture was acidified and distilled. This gave ca. 60% yield of difluoronitromethane (Scheme 5), which was characterised by ^{1}H and ^{13}C NMR. Several methods for preparing difluoronitromethane have been reported,[18–20] but the method described here is very convenient.



Scheme 5. One-pot synthesis of difluoronitromethane (*reagents*: (i) Selectfluor/DBU in DMF, −10 °C to rt, 40 h; (ii) H^+, H_2O.

3. Conclusions

This paper describes improved methods for synthesising heterocycles substituted with a nitroalkyl group and for the conversion of this group in these compounds and others into CCl_2NO_2 and CF_2NO_2. The fluorinated compounds were obtained either using Selectfluor or *N*-fluorobenzenesulfonimide with DBU as base and DCM as solvent. We also describe a one-pot procedure for the preparation of the useful intermediate difluoronitromethane.

4. Experimental

4.1. General

Methyl nitrate was prepared as described.[21] Nitroalkanes and arylnitromethanes were prepared by reaction of the

corresponding bromides with sodium nitrite in DMF.[5] 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor™), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) and other reagents were purchased from Aldrich Chemical Company and were used without further purification. Solvents were dried before use by standard procedures. ^{1}H NMR spectra were recorded at 300 or 500 MHz on Bruker or Jeol spectrometers. ^{13}C NMR spectra were recorded at 75 or 125 MHz. ^{19}F NMR spectra were recorded at 470 MHz. In ^{19}F NMR spectra, upfield shifts are quoted as negative and are referenced to $CFCl_3$. Mass spectra were taken with a Micromass Platform II: EI mode (70 eV). Ultraviolet spectra were obtained by a Shimadzu 160 UV spectrometer. Infrared spectra were taken with a Shimadzu PU 9716 spectrophotometer, Model 435. Medium pressure ('flash') column chromatography was performed using silica (Merck #60). Silica plates (Merck) were used for TLC analysis.

4.2. General procedure for synthesis of nitromethyl- and phenyl-nitromethyl heterocycles

To pre-cooled LDA (1.5 M in THF, 0.8 mL) in dry THF (20 mL) was added the phenylmethyl- or methyl-substituted heterocycle (1 mmol) rapidly at −40 °C. After stirring for 5 min, methyl nitrate (235 mg, 3.5 mmol) was added as rapidly as possible, while the temperature was kept below −40 °C. The mixture was stirred at −40 °C for 1 h and at room temperature for 3–4 h. Filtration gave the crude lithium nitronate. This was taken up in water (20 mL) and the resulting solution was acidified with glacial acetic acid (2 mL) at room temperature. The precipitate was filtered, washed with a little cold water, and recrystallised from 95% ethanol to afford the pure nitro compound.

4.2.1. 2-Nitrobenzylpyridine (1). A/B 0:100; 72% yield, mp 157–159 °C (EtOH). ν_{max} (KBr): 1589 cm^{-1}. λ_{max} (95% EtOH): 255 (ε 50,600 cm^{-1} M^{-1}). ^{1}H NMR spectrum (500 MHz, DMSO-d_6): δ 7.30 (m, 5H, aryl–H), 7.42–7.48 (m, 2H, 2×py–H), 7.92 (dd, J=7.7 and 7.7 Hz, 1H, py–H), 8.67 (d, J=4.3 Hz, 1H, py–H), 11.63 (br s, 1H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 123.0 (CH=NO_2), 125.3, 126.9, 128.4, 128.9, 135.9, 136.4, 149.5, 152.6, 154.7 (aryl–C and py–C). Mass spectrum (EI): m/z (%)=214 (12, M^+), 169 (27, M^+-NO_2), 79 (100), 77 (49). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 67.01; H, 4.30; N, 12.99. R_f=0.58 (petrol/DCM 3:1).

4.2.2. 4-Nitrobenzylpyridine (2). A/B 0:100, 77% yield, mp 187–190 °C (EtOH). ν_{max} (KBr): 1603 cm^{-1}. λ_{max} (95% EtOH): 215 nm (ε 68,900 cm^{-1} M^{-1}), 238 (53,900). ^{1}H NMR spectrum (500 MHz, DMSO-d_6): δ 7.30 (d, J=8.8 Hz, 2H, py–H), 7.39 (m, 5H, aryl–H), 8.69 (d, J=8.8 Hz, 2H, py–H), 11.64 (br s, 1H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 123.0 (HC=NO_2), 126.8, 128.7, 129.4, 135.4, 141.5, 149.9, 153.4 (aryl– and py–C). Mass spectrum (EI): m/z (%)=214 (13, M^+), 169 (20, M^+-NO_2), 79 (100), 77 (50). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.70; N, 13.08. Found: C, 66.98; H, 4.52; N, 13.10. R_f=0.54 (hexane/ethyl acetate 3:2).

4.2.3. 2-Nitromethylpyridine (3). A/B 68:32, 50% yield, bp 70 °C (0.2 mmHg), lit.[9] 70 °C. ν_{max} (KBr): 1575 cm^{-1}. λ_{max} (95% EtOH): 291 nm (ε 52,300 cm^{-1} M^{-1}), 422 (44,200). ^{1}H NMR spectrum (500 MHz, DMSO-d_6): δ 5.60 (s, 1.35H, CH_2NO_2), 6.92 (s, 0.32H, CH=NO_2), 7.58–7.60 (m, 1H, py–H), 7.85–8.36 (m, 2H, py–H), 8.50–8.57 (m, 1H, py–H), 11.63 (br s, 0.54H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 76.3 (CH_2NO_2), 106.4 (HC=NO_2), 112.2, 114.4, 117.6, 125.9, 126.2, 131.4, 138.8, 139.9, 150.8, 151.4 (py–C). Mass spectrum (EI): m/z (%)=138 (20, M^+), 104 (70), 92 (100, M^+-NO_2). R_f=0.36 (hexane/ethyl acetate 3:2).

4.2.4. 4-Nitromethylpyridine (4). A/B 71:29, 64% yield, mp 96–98 °C (EtOH), lit.[9] 97 °C. ν_{max} (KBr): 1367, 1640, 1597 cm^{-1}. λ_{max} (95% EtOH): 295 nm (ε 70,200 cm^{-1} M^{-1}), 429 (44,800). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 5.84 (s, 1.4H, CH_2NO_2), 6.87 (s, 0.3H, CH=NO_2), 7.50–7.60 (m, 2H, py–H), 7.93 (d, J=7.1 Hz, 0.58H, py–H), 8.66–8.68 (m, 1.42H, py–H), 12.10 (br s, 0.3H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 75.8 (CH_2NO_2), 105.5 (HC=NO_2), 111.1, 113.7, 125.4, 132.3, 138.9, 150.5 (py–C). Mass spectrum (EI): m/z (%)=138 (25, M^+), 104 (40), 92 (100, M^+-NO_2). R_f=0.44 (hexane/ethyl acetate 3:2).

4.2.5. 2-Nitromethylquinoline (5). A/B 28:72, 45% yield, mp 120–122 °C (EtOH), lit.[9] 122 °C. ν_{max} (KBr): 1587, 1630, 1348 cm^{-1}. λ_{max} (95% EtOH): 303 nm (ε 13,300 cm^{-1} M^{-1}), 417 (32,400), 439 (39,200). ^{1}H NMR spectrum (500 MHz, DMSO-d_6): δ 6.10 (s, 0.56H, CH_2NO_2), 7.17 (s, 0.72H, CH=NO_2), 7.13–8.51 (m, 6H, py–H), 13.65 (br s, 0.72H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 81.1 (CH_2NO_2), 107.7 (CH=NO_2), 118.7, 119.6, 122.3, 123.4, 125.5, 127.5, 127.6, 128.1, 128.2, 128.9, 130.4, 132.0, 135.7, 137.7, 142.3, 146.6, 147.1, 150.9 (quinoline–C). Mass spectrum (EI): m/z (%)= 188 (6.5, M^+), 154 (68), 142 (100, M^+-NO_2). R_f=0.52 (hexane/ethyl acetate 3:2).

4.2.6. 3-Methyl-2-nitromethyl-4-phenylquinoline (6). A/B 43:57, 75% yield, mp 143–146 °C (EtOH). ν_{max} (KBr): 1619, 1600, 1353 cm^{-1}. λ_{max} (95% EtOH): 305 nm (ε 16,900 cm^{-1} M^{-1}), 417 (32,000), 438 (37,800). ^{1}H NMR spectrum (500 MHz DMSO-d_6): δ 1.93 (s, 1.3H, CH_3, A form), 2.17 (s, 1.7H, CH_3, B form), 6.23 (s, 1.06H, CH_2NO_2), 7.16 (s, 0.5H, CH=NO_2), 7.07–8.04 (m, 9H, aryl–H and py–H), 14.53 (br s, 0.42H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 15.7 (CH_3, A form), 15.7 (CH_3, B form), 80.0 (CH_2NO_2), 106.0 (CH=NO_2), 118.6 (aryl–C), 123.4, 123.9, 125.5, 125.8, 126.4, 126.7, 127.1, 127.6, 128.4, 128.7, 128.9, 128.9, 129.0, 129.2, 129.3, 131.1, 132.2, 135.9, 136.3, 137.1, 145.5, 146.5, 147.5, 149.3, 150.9 (quinoline–C). Mass spectrum (EI): m/z (%)=278 (15, M^+), 232 (100, M^+-NO_2), 219 (35), 201 (35). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.00. Found: C, 73.25; H, 4.89; N, 10.10. R_f=0.54 (hexane/ethyl acetate, 3:2).

4.2.7. 4-Chloro-2-nitromethylquinoline (7). A/B 64:36, 80% yield, mp 118–120 °C (EtOH). ν_{max} (KBr): 1603, 1619, 1383 cm^{-1}. λ_{max} (95% EtOH): 307 nm (ε 21,800 cm^{-1} M^{-1}), 423 (34,700), 446 (38,000). ^{1}H NMR spectrum (500 MHz DMSO-d_6): δ 6.08 (s, 1.28H, CH_2NO_2), 7.10 (s, 0.36H, CH=NO_2), 7.50–8.23 (m, 5H,

aryl–H), 13.35 (br s, 0.36H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 80.3 (CH_2NO_2), 107.8 ($CH{=}NO_2$), 119.2, 121.0, 122.6, 123.8, 124.4, 125.1, 125.6, 126.0, 126.8, 129.2, 129.6, 131.6, 133.1, 142.3, 143.5, 147.9, 150.2, 151.0 (quinoline–C). Mass spectrum (EI): *m/z* (%)=224 (1.8, M^++2), 222 (5.5, M^+), 189 (23), 187 (71), 175 (81, M^+-NO_2), 139.9 (100). Anal. Calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 54.02; H, 3.13, N, 12.58. R_f=0.68 (petrol/diethyl ether 4:1).

4.2.8. 4-Nitromethylquinoline (8). A/B 70:30, 85% yield, mp 135–137 °C (EtOH), lit.[9] 122 °C. ν_{max} (KBr): 1340, 1585, 1625 cm^{-1}. λ_{max} (95% EtOH): 316 nm (ε 32,400 cm^{-1} M^{-1}), 374 (6700), 458 (17,300). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 6.40 (s, 1.4H, CH_2NO_2), 7.45–9.00 (m, 7H, aryl–H and $CH{=}NO_2$), 12.97 (br s, 0.3H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 75.8 (CH_2NO_2), 105.5 ($CH{=}NO_2$), 111.8, 119.8, 124.2, 125.6, 126.7, 129.4, 128.0, 130.5, 131.7, 132.2, 139.1, 139.3, 142.7, 143.9, 146.0, 146.3, 149.8, 150.9 (quinoline–C). Mass spectrum (EI): *m/z* (%)=188 (3, M^+), 154 (70), 142 (100, M^+-NO_2). R_f=0.56 (petrol/diethyl ether 3:1).

4.2.9. 6-Nitromethylphenanthridine (9). A/B 36:64, 80% yield, mp 189–191 °C (EtOH). ν_{max} (KBr): 1600, 1624, 1353 cm^{-1}. λ_{max} (95% EtOH): 245 nm (ε 10,000 cm^{-1} M^{-1}), 413 (10,000), 435 (15,300). ^{1}H NMR spectrum (500 MHz, DMSO-d_6): δ 6.60 (s, 0.36H, CH_2NO_2), 8.05 (s, 0.82H, $CH{=}NO_2$), 7.52–8.72 (m, 8H, aryl–H), 14.10 (br s, 0.82H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 79.3 (CH_2NO_2), 106.2 ($CH{=}NO_2$), 119.2, 120.4, 121.0, 123.0, 123.1, 123.3, 123.4, 125.6, 125.9, 126.0, 128.4, 129.2, 129.4, 129.8, 130.5, 131.4, 131.8, 132.1, 133.0, 133.8, 142.1, 142.6, 145.6, 146.1, 149.5, 150.9 (heteroaryl–C). Mass spectrum (EI): *m/z* (%)=238 (5, M^+), 204 (100), 192 (55). Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.47; H, 4.10; N, 11.95. R_f=0.48 (hexane/ethyl acetate 3:2).

4.2.10. 2-Nitromethylbenzothiazole (10). A/B 15:85, 46% yield, mp 147–148 °C (EtOH), lit.[9] 144 °C. ν_{max} (KBr): 1610, 1595, 1358 cm^{-1}. λ_{max} (95% EtOH): 216 nm (ε 68,100 cm^{-1} M^{-1}), 384 (70,800). ^{1}H NMR spectrum (300 MHz, DMSO-d_6): δ 6.44 (s, 0.15H, CH_2NO_2), 7.70 (s, 0.92H, $CH{=}NO_2$), 7.20–8.20 (m, 4H, aryl–H), 9.10 (s, 0.92H, NH). ^{13}C NMR spectrum (75 MHz, DMSO-d_6): δ 75.0 (CH_2NO_2), 108.0 ($CH{=}NO_2$), 116.1, 118.3, 122.9, 123.8, 127.7, 129.4, 131.5, 133.6, 141.1, 143.0, 152.3, 154.6, 160.4, 161.8. Mass spectrum (EI): *m/z* (%)=194 (4, M^+), 148 (57), 159.9 (100). R_f=0.42 (*n*-hexane/ethyl acetate 3:2).

4.2.11. 2-Nitromethylbenzoxazole (11). A/B 0:100, 18% yield, mp 82–84 °C (EtOH), lit.[9] 76 °C. ν_{max} (KBr): 1616 cm^{-1}. λ_{max} (95% EtOH): 212 nm (ε 57,800 cm^{-1} M^{-1}), 348 (38,800). ^{1}H NMR spectrum (500 MHz, DMSO-d_6): δ 7.30 (s, 1H, $CH{=}NO_2$), 7.31–8.83 (m, 4H, aryl–H), 11.20 (br s, 1H, NH). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 115.0 ($CH{=}NO_2$), 119.0, 132.6, 136.0, 136.1, 143.1, 158.1, 161.2. Mass spectrum (EI): *m/z* (%)=178 (6, M^+), 133 (100, M^+-NO_2), 144 (20). R_f=0.58 (*n*-hexane/ethyl acetate 3:2).

4.3. General procedure for synthesising dichloronitro compounds

To a stirred solution of the nitro compound (1 mmol) in DCM (5 mL) were added DBU (0.015 mL, 0.1 equiv) and *N*-chlorosuccinimide (0.297 g, 2.2 mmol) in DCM (5 mL). After stirring for 2 h the solvent was removed and the residue was purified by 'flash' chromatography on silica (using the solvent system given with the R_f value of each dichloronitro compound).

4.3.1. 1,1-Dichloro-1-nitrooctane (12). Colourless oil. ν_{max} (KBr): 2957, 2930, 2872, 2859, 1584, 1329 cm^{-1}. ^{1}H NMR spectrum (200 MHz, $CDCl_3$): δ 0.82 (t, *J*=7 Hz, 3H, CH_3), 1.25 (m, 8H, $(CH_2)_4$), 1.48 (quintet, *J*=7 Hz, 2H, CH_2) 2.62 (t, *J*=8 Hz, 2H, $CH_2CCl_2NO_2$). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.4, 22.9, 25.5, 28.8, 29.2, 31.9, 46.9, 114.5 (CCl_2NO_2). Mass spectrum (EI): *m/z* (%) 145 (35, $C_8H_{14}{}^{35}Cl^+$). Anal. Calcd for $C_8H_{15}Cl_2NO_2$: C, 40.12; H, 6.63; N, 5.34. Found: C, 39.98; H, 6.52; N, 5.34. R_f=0.18 (petrol/DCM 4:1).

4.3.2. Phenyldichloronitromethane (13). Colourless oil. ν_{max} (KBr): 2940, 1588, 1343, 1321, 815 cm^{-1}. ^{1}H NMR spectrum (200 MHz, $CDCl_3$): δ 7.32 (m, 3H, aryl–H), 7.77 (m, 2H, aryl–H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 114.1 (CCl_2NO_2), 126.9, 128.1, 131.8, 135.7. Mass spectrum (EI): *m/z* (%) 159 (100, M^+-NO_2). Anal. Calcd for $C_7H_5Cl_2NO_2$: C, 40.81; H, 2.45; N, 6.80. Found: C, 40.82; H, 2.45; N, 6.70. R_f=0.70 (petrol/DCM 1:1).

4.3.3. 4-*tert*-Butylphenyldichloronitromethane (14). Colourless oil. ν_{max} (KBr): 2966, 1585, 1395, 1364, 1314, 827, 764 cm^{-1}. (Found: C, 50.90; H, 5.18; N, 5.30. $C_{11}H_{13}Cl_2NO_2$ requires C, 50.40; H, 5.00; N, 5.34%). ^{1}H NMR spectrum (200 MHz, $CDCl_3$): δ 1.26 (s, 9H, $C(CH_3)_3$), 7.40 (d, *J*=10 Hz, 2H, aryl–H), 7.69 (d, *J*=10 Hz, 2H, aryl–H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 31.5, 35.3, 114.6 (CCl_2NO_2), 126.2, 127.1, 133.2, 155.8. Mass spectrum (EI): *m/z* (%) 215 (100, M^+-NO_2), 200 (66), 185 (29). Anal. Calcd for $C_{11}H_{13}Cl_2NO_2$: C, 50.40; H, 5.00; N, 5.34. Found: C, 50.90; H, 5.18; N, 5.30. R_f=0.60 (petrol/DCM 1:1).

4.3.4. (+/−)-2-(2,2-Dichloro-2-nitro-ethoxy)-tetrahydropyran (15). Colourless oil. ν_{max} (KBr): 2946, 2875, 2854, 1588, 1324 cm^{-1}. ^{1}H NMR spectrum (200 MHz, $CDCl_3$): δ 1.53 (m, 6H, CH_2), 3.50 (m, 1H, CH), 3.70 (m, 1H, CH), 4.20 (d, *J*=12 Hz, 1H, CH), 4.46 (d, *J*=12 Hz, 1H, CH), 4.74 (m, 1H, CH). Mass spectrum (EI): *m/z* (%) 244 (1, M^+), 101 (13), 85 (67), 56 (100). HRMS: found (M^+) 243.9978, $C_7H_{12}NO_4Cl_2$ requires 243.9987. R_f=0.57 (DCM).

4.3.5. 1,1-Dichloro-1-nitro-3-phenylpropane (16). Colourless oil. ν_{max} (KBr): 3030, 1581, 1327, 754, 699 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.82 (m, 2H, CH_2), 2.92 (m, 2H, CH_2), 7.20 (m, 5H, aryl–H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 29.5, 46.3, 111.3 (CCl_2NO_2), 125.3, 126.6, 126.9, 136.1. Mass spectrum (EI): *m/z* (%) 187 (100, M^+-NO_2), 91 (66). R_f=0.42 (petrol/DCM 4:1).

4.3.6. (+/−)-2-Chloro-2-nitrooctane (17). Colourless oil. ν_{max} (KBr): 2959, 2934, 2873, 2860, 1560, 1341 cm^{-1}.

^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 0.82 (t, J=7 Hz, 3H, CH_2), 1.32 (m, 8H, CH_2), 2.02 (s, 3H, CH_3), 2.22 (m, 2H, CH_2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.4, 22.8, 24.8, 28.9, 29.7, 31.7, 43.5, 105.2 (CCl_2NO_2). Mass spectrum (EI): m/z (%) 158 (6, M^+-Cl), 111 (32), 43 (64). Anal. Calcd for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; N, 7.23. Found: C, 49.11; H, 8.78; N, 7.03. R_f=0.39 (petrol/DCM 4:1).

4.4. General procedure for fluorination of nitro compounds with Selectfluor

4.4.1. Difluorination of nitro compounds. To a solution of the nitro compound (2.9 mmol) in dry CH_2Cl_2 (25 mL) was added Selectfluor (2.58 g, 7.25 mmol) and the mixture was cooled to 0 °C. DBU (0.928 g, 6.9 mmol) was added and the mixture was stirred for 1 h at 0 °C. After stirring for 3 h at room temperature the mixture was filtered. To the filtrate was added water (50 mL) and the organic layer was separated, washed with brine (50 mL) and 10% sodium hydrogen carbonate (50 mL), and dried over $MgSO_4$. The solvent was removed to give crude product that was purified by 'flash' chromatography on silica, eluting with an appropriate solvent.

4.4.1.1. 1,1-Difluoro-1-nitro-3-phenylpropane (18). Colourless oil. ν_{max} (KBr): 3031, 1586, 1257, 744, 699. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.59 (m, 2H, $CH_2CF_2NO_2$), 2.76 (m, 2H, $CH_2CH_2CF_2$), 7.19 (m, 5H, aryl–H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 27.7 (CH_2), 35.0 (d, $^2J_{CF}$=21 Hz, $CH_2CF_2NO_2$), 124.7 (t, $^1J_{CF}$=279 Hz, CF_2NO_2), 127.0, 128.2, 128.8, 137.6. ^{19}F NMR spectrum (470 MHz, $CDCl_3$): −86.80. Mass spectrum (EI): m/z (%) 203 (6, M^+), 155 (2), 91 (100). HRMS (EI): found (M^+) 201.0596, $C_9H_9NO_2F$ requires 201.0601. R_f=0.48 (petrol/DCM 4:1).

4.4.1.2. 1-Methoxy-4-difluoronitromethyl-benzene (19). Mp 62–64 °C (ethyl acetate). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 3.75 (s, 3H, OCH_3), 6.74 (d, J=8.7 Hz, 2H, C_2–H), 8.77 (d, J=8.7 Hz, 2H, C_3–H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 55.9 (OCH_3), 119.9 (t, J=102 Hz, CF_2NO_2), 128.4, 128.4, 163.7 (aryl–C). ^{19}F NMR (470 MHz, $CDCl_3$): δ −87.0 (s, CF_2NO_2). Mass spectrum (EI): m/z (%) 203 (8, M^+), 157 (100, M^+-NO_2). R_f=0.45 (petrol/diethyl ether 4:1).

4.4.1.3. 4-(*tert*-Butyl)-1-(difluoronitromethyl)-benzene (20). Oil. ν_{max} (KBr): 2967, 1588, 1365, 1384, 1397, 1309, 824 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 1.25 (s, 9H, $C(CH_3)_3$), 7.41 (d, J=8.8 Hz, 2H, C_3–H), 7.59 (d, J=8.8 Hz, 2H, C_2–H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 31.4 (CH_3), 35.5 ($C(CH_3)_3$), 122.6 (t, J=284 Hz, CF_2NO_2), 124.9, 126.3, 126.8, 157.4 (aryl–C). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ 68.6 (s, CF_2NO_2). Mass spectrum (EI): m/z (%) 183 (100, M^+-NO_2), 168 (42), 153 (20). R_f=0.50 (petrol/DCM 4:1).

4.4.1.4. 4-Methylphenyldifluoronitromethane (21). Oil. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.31 (d, J=8.4 Hz, 2H, aryl–*H*), 7.69 (d, J=8.4 Hz, 2H, aryl–H). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 21.2 (CH_3), 124.4 (t, J=35 Hz, CF_2NO_2), 125.6, 129.4, 144.1 (aryl–C). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ −86.99. Mass spectrum (EI): m/z (%) 187 (6.7, M^+), 141 (100, M^+-NO_2). R_f=0.45 (petrol/diethylether 4:1).

4.4.1.5. 4-Chlorophenyldifluoronitromethane (22). Oil. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 7.39 (d, J=8.6 Hz, 2H, aryl–H), 7.58 (d, J=8.6 Hz, 2H, aryl–H). ^{13}C NMR spectrum (300 MHz, $CDCl_3$): δ 140.4, 130.3, 129.9, 128.1, 127.9 (aryl–C), 126.2 (t, J=37 Hz, CF_2NO_2). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ −87.20. Mass spectrum (EI): m/z (%) 207 (1.8, M^+), 161 (100, M^+-NO_2). R_f=0.85 (petrol/diethyl ether 4:1).

4.4.1.6. 1,1-Difluoro-1-nitrooctane (23). Oil. ν_{max} (KBr): 2958, 2932, 2874, 2861, 1586, 1213 cm^{-1}. ^{1}H NMR spectrum (500 MHz, $CDCl_3$): δ 0.81 (t, 3H, CH_3), 1.25 (m, 8H, CH_2), 1.44 (m, 2H, CH_2), 2.28 (tt, J_{HH}=8 Hz, J_{FH}=14 Hz, 2H, $CH_2CF_2NO_2$). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 14.0, 21.4, 22.5, 28.4, 28.7, 31.4, 33.2 (t, $^2J_{CF}$=21 Hz, $CH_2CF_2NO_2$), 125.4 (t, $^1J_{CF}$=289 Hz, CF_2NO_2). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ −86.6 (t, J_{HF}=14 Hz). Mass spectrum (EI): m/z (%) 149 (6, M^+-NO_2), 43 (100). R_f=0.85 (petrol/diethyl ether 4:1).

4.4.1.7. 6-(Difluoronitromethyl)-phenanthiridine (24). Mp 99–101 °C (EtOAc). ^{1}H NMR spectrum (500 MHz, DMSO-d_6): δ 7.25–8.72 (m, 8H, aryl–H). ^{13}C NMR spectrum (125 MHz, DMSO-d_6): δ 124.9 (t, J=18.0 Hz, CF_2NO_2), 121.8, 122.2, 122.9, 124.5, 125.1, 128.9, 129.0, 129.9, 130.8, 131.4, 131.8, 134.0, 144.4 (aryl–C). ^{19}F NMR spectrum (470 MHz, DMSO-d_6): δ −79.59 (s, CF_2NO_2). Mass spectrum (EI): m/z (%) 274 (2.1, M^+), 228 (100, M^+-NO_2). HRMS (EI): found 183.0694 (M^+), $C_9H_{10}NO_2F$ requires 183.0696. R_f=0.25 (petrol/DCM 4:1).

4.4.2. Monofluorination of nitro compounds. Method A: to a stirred solution of the nitro compound (1.0 mmol) in dry DCM (5 mL) cooled to 0 °C, DBU (1.05 mmol) was added followed by addition of Selectfluor (1.25 mmol) in small portions. After stirring for 2 h at room temperature, the reaction mixture was poured into DCM (5 mL), washed with 5% H_2SO_4 (twice) and saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and the solvent was removed. The crude product purified by chromatography on silica eluting with the appropriate solvent (based on R_f value given for TLC).

Method B: to a stirred solution of KOH (1.0 mmol) in dry methanol (5 mL) cooled to 0 °C, were added the nitro compound (1.0 mmol) and Selectfluor (1.1 mmol). The reaction was stirred for 2 h at room temperature and worked up as for Method A.

4.4.2.1. 2-Fluoro-2-nitro-1,3-diphenylpropane (25). Mp 86–88 °C (EtOAc). ν_{max} (KBr): 3032, 1601, 1564, 1369, 1083, 748, 589 cm^{-1}. ^{1}H NMR spectrum (500 MHz, $CDCl_3$): δ 7.35–7.22 (m, 10H, aryl–H), 3.59 (m, 4H, 2×CH_2), 3.40 (t, 2F, CF_2NO_2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 121.3 (d, J=10 Hz, CF_2NO_2), 128.1, 128.7, 130.2, 131.1. Mass spectrum (EI): m/z (%) 259 (10, M^+), 91 (100). Anal. Calcd for $C_{15}H_{15}FNO_2$: C, 69.48; H, 5.44; N, 5.40. Found: C, 69.84; H, 5.29; N, 5.35. R_f=0.50 (ethyl acetate/petrol 1:4).

4.4.2.2. Diphenylfluoronitromethane (26). Mp 44–46 °C (ethyl acetate). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 7.28–8.12 (m, 10H, aryl–H). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 124.8 (d, J=238 Hz, $CFNO_2$), 127.7, 129.1, 130.5, 131.5, 134.6 (aryl–C). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): −104.91 (s, $CFNO_2$). Mass spectrum (EI): m/z (%) 227 (5.4, M^+), 181 (100, M^+-NO_2). R_f=0.80 (petrol/ether 4:1).

4.4.2.3. (+/−)-1-(Fluoronitromethyl)-adamantane (27). Mp 44–46 °C (ethyl acetate). ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 1.56–2.0 (m, 15H, adamantane–H), 5.3 (d, J=50.6 Hz, 1H, $CHFNO_2$). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 27.5, 27.9, 28.1, 28.5, 34.9, 36.4, 36.7, 37.3, 37.5, 40.3 (adamantane–C), 117.4 (d, J=240 Hz, CHFNO$_2$). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ −139.10. Mass spectrum (EI): m/z (%) 203 (1.3, M^+), 157 (100, M^+-NO_2). R_f=0.85 (petrol/diethyl ether 4:1).

4.4.2.4. (+/−)-1-Fluoro-1-nitrooctane (28). Colourless oil. ν_{max} (KBr): 2957, 2931, 2859, 1574, 1384 cm^{-1}. ^{1}H NMR spectrum (500 MHz, $CDCl_3$): δ 0.82 (t, J=8.7 Hz, 3H, CH_3), 1.24 (m, 8H, CH_2), 2.09 (m, 2H, CH_2CHFNO_2), 5.73 (dt, 1H, $CHFNO_2$, J_{HF}=52 Hz, J_{HH}=8 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 111.24 (d, CHFNO$_2$, $^1J_{CF}$=239 Hz), 33.17 (d, CH_2CHFNO_2, $^2J_{CF}$=20 Hz), 31.50, 28.78, 28.59, 22.73, 22.51 (CH_2), 13.98 (CH_3). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ 8.32 (dt, $^2J_{HF}$=52 Hz, $^3J_{HF}$=22 Hz). Mass spectrum (EI): m/z (%) 87 (12, $C_5HH_6F^+$), 73 (14, $C_4H_6F^+$), 59 (15, $C_3H_4F^+$), 57 (53, $C_5H_{11}^+$), 43 (100, $C_3H_7^+$). Anal. Calcd for $C_8H_{16}FNO_2$: C, 54.22; H, 9.10; N, 7.90. Found: C, 53.96; H, 9.34; N, 7.75. R_f=0.39 (petrol/DCM 4:1).

4.4.2.5. (+/−)-2-Fluoro-2-nitrooctane (29). Colourless oil. ν_{max} (KBr): 2959, 2933, 2872, 1564, 1385 cm^{-1}. ^{1}H NMR spectrum (500 MHz, $CDCl_3$): δ 0.81 (t, J=7.0 Hz, 3H, CH_3), 1.21 (m, 8H, CH_2), 1.80 (d, 3H, CH_3 $^2J_{CF}$=22 Hz), 2.03 (m, 2H, CH_2). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 120.26 (d, CFNO$_2$, $^1J_{CF}$=239 Hz), 37.95 (d, CH_2, $^2J_{CF}$=22 Hz), 31.31, 28.53, 23.80 (d, $^2J_{CF}$=24 Hz, CH_3), 22.34 (CH_2), 13.92 (CH_3). ^{19}F NMR spectrum (470 MHz, $CDCl_3$): δ 35.04 (sextet, J=19 Hz). Mass spectrum (EI): m/z (%) 162 (1, M^+-CH_3), 131.0 (1, M^+-NO_2), 111.0 (33, $C_8H_{15}^+$). R_f=0.49 (petrol/DCM 4:1).

4.4.2.6. 1,1-Difluoronitromethane. To a stirred solution of 2-nitroacetophenone[22] (4.84 g, 29.3 mmol) in dry DMF (20 mL) at 0 to −5 °C under nitrogen was added dropwise DBU (8.93 g, 58.7 mmol) in DMF (10 mL) and finally Selectfluor (26.0 g, 73.3 mmol) as a solid. After 40 h at room temperature, water (1 mL, 55 mmol) was added and the mixture was stirred for 2 h. Aqueous HCl (6 M, 5 mL) was added giving a white suspension that was stirred for 2 h. Further aqueous HCl (5 M, 8 mL) and water (20 mL) were added and the mixture was distilled under a flow of nitrogen (bath temperature up to ca. 90 °C). The distillate of difluoronitromethane (2.0 g, 67%, bp ca. 40 °C (lit.[18,19] bp 42 °C at 760 mm) was collected in dry ice. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 6.47 (t, $^2J_{HF}$ 60 Hz). ^{13}C NMR spectrum (125 MHz, $CDCl_3$): δ 113.0 (t, $^1J_{CF}$ 287 Hz).

Acknowledgements

We are thankful to the EPSRC, Isfahan University Research Council, Phoenix Chemicals (Bromborough, UK) and World Health Organisation for support of this work.

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