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Sonochemical fluorination of heterocyclic nitro compounds with Selectfluor☆

Majid M. Sadeghi,[a] Hossein Loghmani-Khouzani,[a,*] Reza Ranjbar-Karimi,[a] Philip Butler[b] and Bernard T. Golding[b,*]

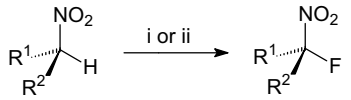
[a]*Department of Chemistry, Isfahan University, Isfahan 81746-73441, Iran*
[b]*School of Natural Sciences—Chemistry, Bedson Building, Newcastle University, Newcastle upon Tyne NE1 7RU, UK*

Abstract—Methine and methylene groups attached to a nitro function and heterocycle (and Ph for CH) were rapidly mono- or di-fluorinated by reaction with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis-tetrafluoroborate (Selectfluor) in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), preferably with ultrasonic irradiation.

Incorporation of fluorine selectively into organic molecules has provided a challenge to academic and industrial research.[1–3] Electrophilic sources of fluorine have been developed for introducing fluorine at centres of high electron density, and offer alternative strategies, where nucleophilic and free radical sources of fluorine have proved inefficient or have failed. Reagents used as a source of 'F^+' include acetyl hypofluorides,[4] *N*-fluoroperfluoropiperidine,[5] dihydro-*N*-fluoro-2-pyridone,[6] *N*-fluoro-*N*-alkylsulfonamides,[7] *N*-fluoropyridinium salts,[8] *N*-fluoroquinuclidinium salts,[9] 1-fluoro-substituted 1,4-diazoniabicyclo[2.2.2]octane salts,[10] 1,4-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts,[11] 1,1′-difluorobipyridinium salts,[12] trifluoroamine oxide[13] and 1-fluoro-2,4,6-trichloro-1,3,5-triazinium tetrafluoroborate.[14]

Reactions of carbanions with *N*-F reagents are generally easier than those with neutral nucleophilic substrates. Thus, fluorination of carbanions adjacent to CO,[15–18] CS,[19] COOR,[16,17] RSO_2,[20,21] NO_2,[22] CN,[8] $PO(OR)_2$ has been reported,[23] although the *N*-F reagent 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2,2,2]-octane bis-tetrafluoroborate (Selectfluor) has also been shown to react with (*E*)-stilbene[24] and saturated hydrocarbons.[25] Electrophilic fluorination of carbanions within the side chains of imidazoles and indoles has been accomplished.[26,27] Recently, Peng and Shreeve reported the fluorination of carbanions from several nitro and cyano compounds using Selectfluor.[28] Most of these reactions, which utilised, for example, potassium hydroxide as base for the nitro compounds, gave mainly products of mono-fluorination.

In this letter we report fluorination of various nitro compounds under two sets of reaction conditions: one consisted of stirring the nitro compound for 4–6 h in the presence of DBU and 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis-tetrafluoroborate (Selectfluor) (Scheme 1); the other conditions employed ultrasonic irradiation in the presence of ammonium acetate as a base and again using Selectfluor (Scheme 1).[29] The latter conditions gave a dramatic acceleration for mono- and di-fluorination and led to high yields of products (Table 1). Ultrasonic irradiation therefore provides the best conditions for the preparation of



Scheme 1. Reagents and conditions: (i) DBU, Selectfluor, CH_2Cl_2; 4–6 h, rt; (ii)))), CH_3COONH_4, Selectfluor, MeOH, 10–15 min, rt (n.b. all chiral compounds were racemic).

Keywords: Heterocycles; Nitro compounds; DBU; Selectfluor; Ultrasonic.
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* Corresponding authors. Tel.: +98 311 7932722; fax: +98 311 6689732 (H.L.-K.); tel.: +44 191 2226647; fax: +44 191 2226929 (B.T.G.); e-mail addresses: h.log119@sci.ui.ac.ir; b.t.golding@ncl.ac.uk

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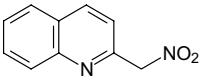
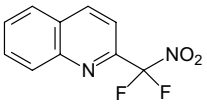
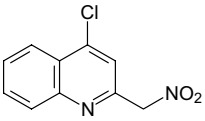
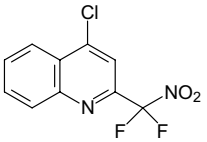
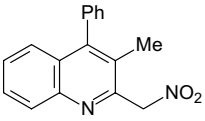
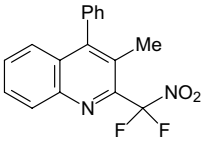
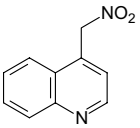
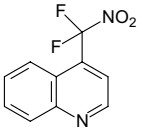
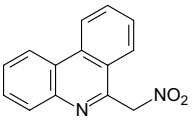
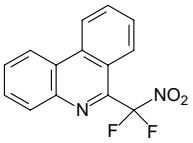
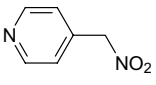
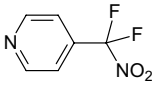
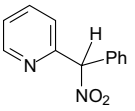
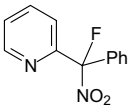
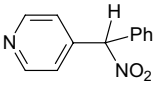
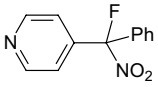
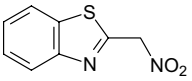
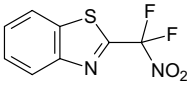
Table 1. Side-chain fluorination of selected heterocyclic compounds

Entry	Nitro compound	Product	^{19}F NMR (ppm)	Yield (%) (time/h)[a,c]	Yield (%) (time/min)[b,c]
1			−87.53	50 (4)	97 (10)
2			−87.89	55 (4)	98 (10)
3			−81.00	50 (5)	98 (10)
4			−83.76	60 (4)	96 (10)
5			−79.59	85 (4)	98 (10)
6			−89.03	54 (4)	95 (15)
7			−113.07	10 (6)	20 (15)
8			−109.27	10 (6)	25 (15)
9			−82.32	50 (5)	96 (10)

[a] Conditions: (i) DBU, Selectfluor, CH_2Cl_2.
[b] Conditions: (ii)))))), Selectfluor, CH_3COONH_4, MeOH.
[c] Isolated yield of spectroscopically characterised pure compound.

mono- and di-fluoro nitro compounds in a short time and in high yield.

In conclusion, the use of ultrasound enabled the easy preparation of organofluorine compounds containing the little investigated CF_2NO_2 group. The advantages of ultrasound in fluorination are shorter reaction times and higher yields. Further chemistry and applications of the CF_2NO_2 group will be reported elsewhere.

Acknowledgements

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29. General procedures for the fluorination of $CHNO_2$ and CH_2NO_2 groups in heterocyclic compounds with Selectfluor: *Conditions (i)*: To a solution of the nitro compound (2.9 mmol) in dry CH_2Cl_2 (25 mL) cooled to 0 °C was added Selectfluor (7.25 mmol, 2.58 g) followed by DBU (6.9 mmol, 0.928 g). After 1 h, the temperature was raised to room temperature and stirring was continued for 3 h. The mixture was cooled in ice-water and filtered, and water (50 mL) was added. The organic layer was separated, washed with brine (50 mL) and saturated aqueous sodium hydrogen carbonate (50 mL), dried over $MgSO_4$, filtered and the solvent was removed The product was purified on a silica column eluted with the appropriate mixture of dichloromethane and petrol. *Conditions (ii)*: To a solution of the nitro compound (2.9 mmol) in dry MeOH (10 mL) was added Selectfluor (7.25 mmol 2.58 g) and ammonium acetate (6 mmol, 0.46 g). The reaction mixture was irradiated with ultrasound for 10–15 min. The mixture was filtered and water (50 mL) and CH_2Cl_2 (30 mL) were added. The organic layer was separated, washed with brine (50 mL), dried over $MgSO_4$, filtered and the solvent was removed. The product was purified on a silica column eluted with the appropriate mixture of dichloromethane and petrol. *2-(Difluoronitromethyl)-quinoline (entry 1)*: mp 49–52 °C, GC–MS (EI) 224 (M^+), 178 (M^+-NO_2), 128 ($M^+-CF_2NO_2$). ^{1}H NMR: δ 7.12–8.55 (m, 6H). ^{19}F NMR (470 MHz, DMSO-d_6): δ −87.53; ^{13}C NMR (125 MHz, DMSO-d_6): δ 117.1 (t, $J = 9.5$ Hz), 127.8, 129.1, 129.3, 130.1, 131.2, 138.5, 145.9, 147.1. *4-Chloro-2-(difluoro-nitromethyl)-quinoline (entry 2)*: mp 57–59 °C, GC–MS (EI) 258 (M^+), 212 (M^+-NO_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.42–8.32 (m, 5H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −87.89; ^{13}C NMR (125 MHz, DMSO-d_6): δ 118.2 (t, $J = 11.0$ Hz), 122.2, 123.9, 125.2, 126.0, 129.2, 133.4, 143.3, 148.9, 154.0. *2-(Difluoronitromethyl)-3-methyl-4-phenylquinoline (entry 3)*: The starting material for this compound (2,3-dimethyl-4-phenylquinoline) was prepared by the literature method.[30] mp 64–68 °C, GC–MS (EI): 314 (M^+), 268 (M^+-NO_2), 218 ($M^+-CF_2NO_2$). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.36 (3H, t, $J = 2.2$ Hz), 7.21–8.06 (m, 9H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −81.00; ^{13}C NMR (125 MHz, DMSO-d_6): δ 15.2, 126.2 (t, $J = 6$ Hz), 128.6, 128.8, 128.9, 129.1, 129.2, 129.8, 130.1, 135.9, 144.3, 144.6, 144.8, 150.7. *4-(Difluoronitromethyl)-quinoline (entry 4)*: mp 42–47 °C, GC–MS (EI) 224 (M^+), 178 (M^+-NO_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62–9.01 (m, 6H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −83.76; ^{13}C NMR (125 MHz, $CDCl_3$): δ 119.9 (t, $J = 28.5$ Hz), 121.4, 123.0, 129.1, 130.9, 131.4, 131.5, 131.7, 148.9 149.3. *6-(Difluoronitromethyl)-phenanthridine (entry 5)*: mp 99–101 °C, GC–MS (EI) 274 (M^+), 228 (M^+-NO_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.25–8.72 (m, 8H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −79.59; ^{13}C NMR (125 MHz, DMSO-d_6): δ 121.8, 122.1, 122.2, 122.9, 124.5, 124.9 (t, $J = 18.0$ Hz), 128.9, 129.0, 129.9, 130.8, 131.4, 131.8, 134.0, 144.4. *4-(Difluoronitromethyl)-pyridine (entry 6)*: Yellow oil, GC–MS (EI) 174 (M^+), 128 (M^+-NO_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 2H), 8.85 (m, 2H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −89.03; ^{13}C NMR (75 MHz, $CDCl_3$): δ 120.1 (t, $J = 33.5$ Hz), 124.3, 135.8 (t, $J =$ 176 Hz), 151.4. *2-Fluoronitro-phenylpyridin-2-ylmethane (entry 7)*: mp 70–73 °C, GC–MS (EI) 232 (M^+), 186 (M^+-NO_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.32–8.67 (m, 9H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −113.07; ^{13}C NMR (125 MHz, DMSO-d_6): δ 124.0, 126.3, 128.2, 130.0 (d, $J = 11.5$ Hz), 130.9, 133.1, 139.5, 142.6, 148.3, 150.5. *4-Fluoronitro-phenylmethylpyridin-4-ylmethane (entry 8)*: mp 103–105 °C, GC–MS (EI) 232 (M^+), 186 (M^+-NO_2). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.30–8.81 (m, 9H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −109.27; ^{13}C NMR (125 MHz, DMSO-d_6): δ 127.0, 128.3 (d, $J = 9.5$ Hz), 129.1, 129.9, 135.5, 144.7, 149.5, 153.9. *2-(Difluoro-nitromethyl)-benzothiazole (entry 9)*: Yellow oil, GC–MS (EI) 230 (M^+), 184 (M^+-NO_2), 134 ($M^+-CF_2NO_2$). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.21–8.42 (m, 4H); ^{19}F NMR (470 MHz, DMSO-d_6): δ −82.32; ^{13}C NMR (125 MHz, DMSO-d_6): δ 117.5 (t, $J = 23.0$ Hz), 121.9, 127.8, 128.2, 135.6, 152.2, 153.4, 153.9.
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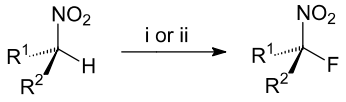
Graphical abstract

Sonochemical fluorination of heterocyclic nitro compounds with Selectfluor

Majid M. Sadeghi, Hossein Loghmani-Khouzani,* Reza Ranjbar-Karimi, Philip Butler and Bernard T. Golding*



Conditions: (i) DBU, 'Selectfluor, CH_2Cl_2, 4–6 h, rt; (ii))))), CH_3COONH_4, Selectfluor, MeOH, 10–15 min, rt.