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One Pot Synthesis of Side Chain Fluorinated Heterocyclic Compounds by Microwave Irradiation

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2- Or 4-Difluoronitromethyl and 2- or 4-fluoronitrobenzyl substituted pyridines, quinolines, phenantheridine, benzothiazol and benzoxazol were synthesized by reaction of the corresponding nitro compounds in the presence of 1-chloromethyl-4-fluoro-1,4-diazoiabicyclo[2,2,2]octane bis(tetrafluoroborate) (Select-Fluor) and ammonium acetate as a base under microwave irradiation. This method is very efficient and the yields were significantly improved in comparison to the previous reports.

Keywords: Heterocyclic compounds, Ammonium acetate, Select-Fluor, Fluorination, Organofluorine, Microwave

INTRODUCTION

The introduction of fluorine into organic compounds is one of the largest projects in the chemical industries and laboratories, since replacement of C-H bonds by C-F bonds strongly affects the physical properties and biological activities of organic compounds [1]. Several methods have been reported for fluorination of organic compounds [2-20]. Although the direct fluorination by elemental fluorine has been investigated by several researchers [2], there are still some problems with the fluorine radical. This radical is quite indiscriminate in the reaction of organic compounds. In recent years, micro reactors have been designed to control direct fluorination processes [2].

The reaction of fluoride ion with appropriate organic compounds is another way for the preparation of organofluorine compounds, and so far many reagents such as diethylaminosulfurtrifluoride (DAST) have been widely used in this respect [3]. Electrophilic fluorination is an interesting alternative method for the cases where fluoride ion and direct fluorination proves to be inefficient. Among electrophilic fluorinating agents, N-F reagents are safe and easy to handle without the need for special equipments. Electron withdrawing effects of fluorine and presence of an excellent leaving group adjacent to fluorine is a common character of these reagents. The best reagents in this category include 1-fluoro-substituted 1,4-diazoniabicyclo[2.2.2]octane salts [4], 1,4-difluoro-1,4-diazoniabicyclo[2.2.2]octane salts [5], 1,1'-difluoro-bipyridinium salts [6], trifluoroamine oxide [7] and 1-fluoro-2,4,6-trichloro-1,3,5-triazinium tetrafluoroborate [8].

Reactions of many carbanions containing useful functional groups such as CO [9-12], CS [13], COOR [10,11], RSO_2 [14, 15] NO_2 [16], CN [8], $PO(OR)_2$ [17] with NF reagents have been investigated in the recent years. Microwave irradiation is well known for the synthesis of various organic compounds [18-20].

EXPERIMENTAL

Chemicals and Apparatus

1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor, F-TEDA-BF_4) was

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purchased from Aldrich and used without further purification. All nitro compounds were synthesized from the corresponding methyl or benzyl substituted heterocyclic compounds according to the literatures [21,22]. ^{1}H NMR spectra were recorded at 500 MHz on a Bruker AC 80 spectrometer. ^{13}C NMR and ^{19}F NMR spectra were recorded at 125 and 470 MHz, respectively. In ^{19}F NMR spectra, the upfield shifts are quoted as negative and are referenced to $CFCl_3$. Mass spectra were recorded on Platlform II Micromass. Column chromatography was performed using silica gel (Merck No 60) and silica plates (Merck) were used for TLC analysis.

General procedure

Nitro compound (3 mmol), Select-luor (6.5 mmol 2.58 g), methanol (1 ml) and ammonium acetate (3 mmol) were placed in a domestic microwave oven. The reaction mixture was irradiated for the times specified in **Table 1**. The mixture was filtered and water (50 ml) was added to the filtrate. The organic layer was separated then washed with brine (50 ml) and sodium hydrogen carbonate 10% (50 ml) and dried over $MgSO_4$. The solvent was evaporated to obtain the crude product. The product was purified by column chromatography using a silica column eluted with appropriate mixture of dichloromethane and petroleum ether.

2-(Difluyoronitromethyl)-quinoline (1). Yield: 55%; M.p.: 49-52 °C; MS (EI, 70 eV): m/z (%): 224 (M, 2.19), 178 (M-NO_2, 4.86), 128 (M-CF_2NO_2, 100); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.12-8.55 (m, aryl-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 117.11 (t, J = 9.50 Hz, **C**F_2NO_2), 127.76, 129.09, 129.25, 130.05, 131.21, 138.45, 145.86, 147.13 (aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): δ -87.53 (s, C**F**$_2NO_2$).

4-Chloro-2-(difluoronitromethyl)-quinoline (2). Yield: 54%; M.p.: 57-59 ^{o}C; MS (EI, 70 eV): m/z (%): 258 (M, 2.2), 212 (M-NO_2, 70); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.42-8.32 (m, aryl-**H**); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 118.23 (t, J = 11.00 Hz, **C**F_2NO_2), 120.92, 122.24, 123.78, 124.38, 125.15, 126.00, 129.22, 132.64, 133.38, 143.25, 148.93, 154.01 (aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): δ -87.89 (s, C**F**$_2NO_2$).

3-Methyl-(2-difluoronitromethyl)-4-phenyl-quinoline (3). Yield: 52%; M.p.: 64-68 ^{o}C; MS (EI, 70 eV): m/z (%): 314 (M, 19), 268 (M-NO_2, 74), 218 (M-CF_2NO_2, 54); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 2.36 (t, 3H, J = 2.2), 7.21-8.06 (m, aryl-**H**); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 15.17 (t, J = 16.40 Hz, **C**H3), 126.16, 126.20 (t, J = 6 Hz, **C**F_2NO_2), 128.60, 128.77, 128.94, 129.11, 129.15, 129.78, 130.10, 135.91, 144.34, 144.55, 144.76, 144.80, 150.69 (aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): δ -81.00 (s, C**F**$_2NO_2$).

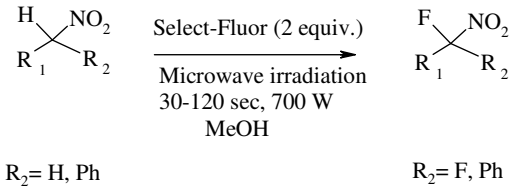
4-(Difluoronitromethyl)-quinoline (4). Yield: 60%; M.p.: 42-47 ^{o}C; MS (EI, 70 eV): m/z (%): 224 (M, 3.5), 178 (M-NO_2, 100); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 7.62 (t, 1H, $J_{5,6}$ = 8.55 Hz C_6**H**), 7.73 (t, 1H, $J_{6,7}$ = 7.3 Hz C_7**H**), 7.77 (d, 1H, $J_{2,3}$ = 4.6 Hz C_3**H**), 8.01 (d, 1H, $J_{5,6}$ = 8.55 Hz C_5**H**), 8.15 (d, 1H, $J_{7,8}$ = 8.55 Hz C_8**H**), 9.01 (d, 1H, $J_{2,3}$ = 4.55 Hz C_2**H**); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 119.90 (t, J = 28.5 Hz, **C**F_2NO_2), 121.40, 122.99, 129.14, 130.56 130.89, 131.16, 131.36, 131.54, 148.85, 149.31 (aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): δ -83.76 (s, C**F**$_2NO_2$).

Difluoronitromethylphenanthiridine (5). Yield: 85%; M.p.: 99-101 ^{o}C; MS (EI, 70 eV): m/z (%): 274 (M, 2.1), 228 (M-NO_2, 100); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.25-8.72 (m, aryl-**H**); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 124.90 (t, J = 18, **C**F_2NO_2), 121.78, 122.07, 122.24, 122.94, 124.54, 125.15, 128.46, 128.96, 129.01, 129. 57, 129.88, 130.75, 131.36, 131.77, 134.03, 141.55, 144.37 (aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): δ -79.59 (s, C**F**$_2NO_2$).

4-(Difluoronitromethyl)-pyridine (6). Yield: 55% oil; MS (EI, 70 eV): m/z (%): 174 (M, 2.1), 128 (M-NO_2, 100); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.63 (dd, 2H, J = 1.6 Hz C_3-**H**), 8.85 (d, 2H, J = 6.13 Hz C_2-**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 120.13 (t, J = 33.5 Hz, **C**$_3$H), 124.32 (**C**$_4$), 135.77 (t, J = 176 Hz, **C**F_2NO_2), 151.37 (s, **C**$_2$H). ^{19}F NMR (470 MHz, $CDCl_3$): δ -89.03 (s, C**F**$_2NO_2$).

2-Fluoronitrobenzylpyridine (7). Yield: 15%; M.p.: 70-73 ^{o}C; MS (EI, 70 eV): m/z (%): 232(M, 15), 186 (M-NO_2, 80); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.32-8.67 (m, aryl-**H**); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 124.00, 126.29 128.23, 130.00 (d, J = 11.5, **C**FNO_2), 130.023, 130.97, 133.06, 148.30(aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): δ -113.07 (s, C**F**NO_2).

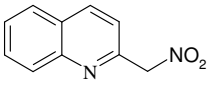
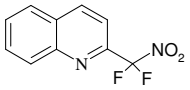
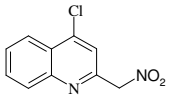
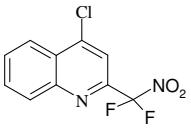
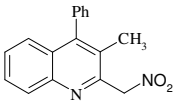
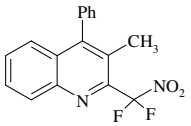
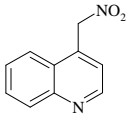
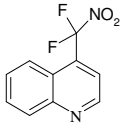
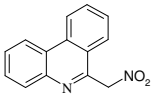
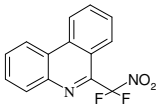
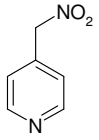
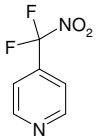
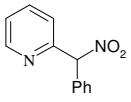
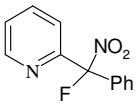
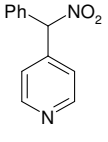
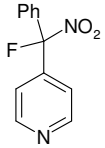
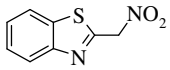
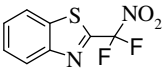
4-Fluoronitrobenzylpyridine (8). Yield: 10%; M.p.: 103-105 ^{o}C; MS (EI, 70 eV): m/z (%): 232 (M, 4.8), 186 (M-NO_2, 20); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.30-8.81 (m, aryl-**H**); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 127, 128.25 (d, J = 9.50, **C**FNO_2), 128.88, 128.99, 129.14, 129.95,



R_2= H, Ph R_2= F, Ph

Scheme 1

Table 1. Some of the Side Chain Fluorinated Heterocyclic Compounds Prepared

Entry	Nitro Comp.	Product	Time (sec)	Yield (%)
1			30	55
2			30	54
3			30	60
4			30	65
5			30	85
6			30	52
7			120	10
8			120	15
9			40	58

135.50, 135.70, 144.27, 144.73, 149.34, 149.54, 153.63, 153.94 (aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): δ -109.27 (s, C**F**NO_2).

2-Difluoronitromethylbenzothiazole (9). Yield: 57% oil; MS (EI, 70 eV): m/z (%): 230 (M, 5), 184 (M-NO_2, 80), 134 (M-CF_2NO_2); ^{1}H NMR (500 MHz, DMSO-d_6): δ (ppm) 7.21-8.42 (m, aryl-**H**); ^{13}C NMR (125 MHz, DMSO-d_6): δ (ppm) 117.51 (t, J = 1119, **C**F_2NO_2), 121.87, 122.13, 125.34, 127.82, 127.99, 128.10, 128.24, 135.59, 152.17, 153.44, 153.70, 153.95 (aryl-**C**); ^{19}F NMR (470 MHz, DMSO-d_6): -82.32 (s, **C**F_2NO_2).

RESULTS AND DISCUSSION

In this research 2- or 4-difluoronitromethyl and 2- or 4-fluoronitrobenzyl substituted pyridines, quinolines, phenantheridine, benzothiazol and benzoxazol were synthesized by reaction of the corresponding nitro compounds in the presence of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) (Select-Fluor) and ammonium acetate as a base under microwave irradiation in good to high yield (Scheme 1, Table 1). The nitro compounds were efficiently synthesized by deprotonation of the corresponding methyl or benzyl substituted heterocyclic compounds with lithium diisopropylamide (LDA) followed by addition of methyl nitrate in THF (yields 46-85%) [21].

CONCLUSIONS

The rate of electrophilic fluorination is very fast under microwave irradiation. Furthermore, difluorination of side chain nitrated heterocyclic compounds with 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Select-Fluor) is achieved successfully in one pot reaction.

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