Effective and Versatile Functionalisation of Hexamethylbenzene Using N-F Reagents

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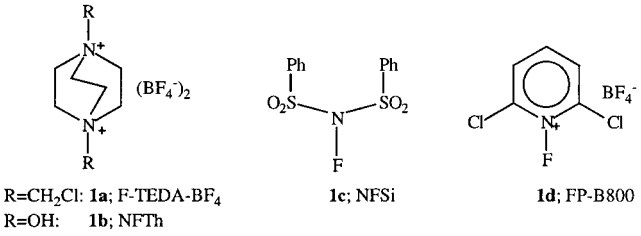
Abstract: Effective direct introduction of alkoxy, amido, azido or halogeno functional groups on the benzylic position in hexamethylbenzene was mediated by the N-F reagents F-TEDA-BF_4, NFTh, NFSi or FP-B800 in the presence of alcohols, carboxylic acids, cyanides or trimethylsilyl derivatives as sources of an external nucleophile.

Key words: N-F reagents, hexamethylbenzene, fluorine, amides, ethers



R=CH_2Cl: **1a**; F-TEDA-BF_4 **1c**; NFSi **1d**; FP-B800
R=OH: **1b**; NFTh

Scheme 1

The introduction of a variety of organic molecules incorporating a reactive N-F bond as versatile, selective, "electrophilic" fluorinating reagents[1] is one of the most important breakthroughs in the field of organic chemistry of fluorine compounds in the last decade.[2] However, N-F compounds also possess an oxidative power, which, although lower in comparison with other types of "electrophilic" fluorinating regents,[3] is still high enough perhaps to cause a certain competition between fluorination and oxidation of the target molecule, diminishing the selectivity of functionalisation.

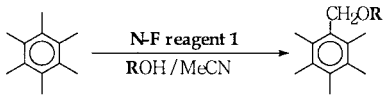
Alkyl-substituted aromatic molecules were often used as models for evaluation of electrophilic fluorinating reagents since they possess three main potential reactive sites: the unsubstituted and *ipso* position on the aromatic ring, and the benzylic position on the side chain. These reactions were intensively studied in the case of fluoroxy reagents[4] and xenon difluoride,[5] where the selectivity of functionalisation, mainly fluorination, was strongly dependent on the structure of the target molecule and the reaction conditions, while for the N-F reagents such reports are scarce.[6] As a part of our continuing interest in the reactions of N-F reagents with organic molecules we now report the application of this type of compounds as effective mediators of a variety of direct functionalisations of hexamethylbenzene.

From three types of N-F reagents we chose four commonly used and commercially available reagents: 1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**1a**, Selectfluor™ F-TEDA-BF_4) and 1-fluoro-4-hydroxy-1,4-diazoniabicyclo [2.2.2]octane bis(tetrafluoroborate) (**1b**, Accufluor™ NFTh) from the $F\text{-}N^+R^1R^2R^3Y^-$ type, *N*-fluorobenzenesulfonimide (**1c**, Accufluor™ NFSi) from the R^1R^2N-F type, and *N*-fluoro-2,6-dichloropyridinium tetrafluoroborate (**1d**, FP-B800) as a representative of the *N*-fluoro pyridinium salts.[7]

In a typical experiment we treated hexamethylbenzene (HMB, **2**, Table) with N-F reagent **1** in acetonitrile solution, but the isolated reaction mixtures were in all four cases too complex and irreproducible to have any synthetic value. However, by adding an at least five-fold molar excess of methanol to the reaction mixture, we readily isolated pentamethylbenzylmethyl ether in high to almost quantitative yield, depending on the N-F reagent used.[7] Encouraged with this result we tested the reaction with a variety of alcohols and established that pentamethylbenzyl ethers **3**, could also be obtained with long chain *n*-alcohols (**3a**), *iso* (**3b**), cyclic (**3c**), and benzyl alcohols (**3f**), as well as with alcohols bearing electron donating (**3d**) or withdrawing (**3e**) functional groups (Table). Unfortunately, the reaction did not work with *tert*-alcohols. The best results of this direct alkoxy functionalisation of the benzylic position were obtained using F-TEDA-BF_4 as the mediator, moderate to good yields were also accomplished by NFTh, while NFSi and FP-B800 were less effective.

Another type of functionalisation was achieved when we reacted HMB with N-F reagents **1** in acetonitrile solution in the presence of trifluoroacetic acid.[7] Under these acidic conditions quantitative conversion of HMB to pentamethylbenzylacetamide **4** (R = Me, Table 1) took place. We further applied this N-F reagent mediated Ritter-type[8] reaction for the effective synthesis of a series of pentamethylbenzylamides **4** from the corresponding cyanides, using TFA as solvent and at least a threefold molar excess of cyanide. Good to excellent results were obtained with *n*-alkyl cyanides (**4b**), with *iso*- (**4c**) and cycloalkyl cyanides (**4d**), with cyanides bearing electron donating (**4e**) or withdrawing (**4f**) groups, as well as with phenyl (**4h**) or benzyl cyanides (**4j**). Again, the best results were achieved using F-TEDA-BF_4 as mediator, NFSi and

Table The effect of reaction conditions and the structure of N-F reagent **1** on the functionalisation of hexamethylbenzene **2**.



2 **3**

Product	R	Reaction time (h) 1a	1b	1c	1d	Yield (%) 1a	1b	1c	1d	m.p. (°C)
3a	$CH_3(CH_2)_4CH_2$	1	1			90	68			liquid
3b	iPr	1	1	20	1	88	55	< 2	43	liquid
3c	cyclopenthyl	1	1	20	20	98	95	38	15	52.4 – 53
3d	$MeOCH_2CH_2$	1	1	48	2	93	88	22	< 2	liquid
3e	CF_3CH_2	1				75				70-72
3f	$PhCH_2$	3				75				62.5 - 63
	2 + 1 / RCN / TFA ⟶ $(CH_3)_5PhCH_2NHCOR$ **4**									
4a	CH_3CH_2	2	27	6	2	82	60	68	67	221–221.5
4b	$CH_3(CH_2)_3CH_2$	3				65				174.5-175
4c	iPr	2	50	2	2	75	67	51	59	225-226
4d	cyclopropyl	1	24	5	2	86	50	92	62	257 - 258
4e	CH_3OCH_2	1	33	3	2	95	53	89	87	130– 131
4f	$MeOOCCH_2$	1				98				165.5-166
4g	$EtOOCCH_2$	1				84				161-163
4h	Ph	1				75				200-201
4i	p-MeOOCPh	1				71				213-214
4j	$PhCH_2$	1	33	3	2	90	62	82	83	207-208
	2 + 1 / TMSR / MeCN ⟶ $(CH_3)_5PhCH_2R$ **5**									
5a	N_3	3	3	24	1	96	72	33	65	66-66.5
5b [9]	Cl	4	4	24	2	80	83	42	84	81-82
	2 + 1 / RCOOH ⟶ $(CH_3)_5PhCH_2OCOR$ **6**									
6a [9]	CH_3	72	72	72	1	97	26	99	57	84-86
6b [5a]	CF_3	1	22	19	1	99	42	15	80	94-96

FP-B800 gave also good results, while in this case NFTh was less effective.

We also applied trimethylsilyl derivatives as a source of the nucleophile and readily functionalised HMB at the benzylic position with azido (**5a**), chloro (**5b**) or acetoxy (**6a**) groups.[7] Pentamethylbenzyl acetate **6a** or pentamethylbenzy trifluoroacetate **6b** were also quantitatively obtained when we treated HMB with F-TEDA-BF_4 in acetic or trifluoroacetic acid, respectively.

We established that by using appropriate reaction conditions and F-TEDA-BF_4 as mediator, selective functionalisation of HMB can also be obtained in the presence of compounds bearing two different nucleophilic centres (Scheme 2). When we used TFA as solvent, cyanoacetic acid as a source of external nucleophile was activated at its cyanide moiety and the corresponding benzyl amide, i.e. 3-oxo-3-[(pentamethylbenzyl)amino]propanoic acid **7**, was isolated, while in MeCN potassium cyanoacetate acted as a carboxy nucleophile and pentamethylbenzyl cyanoacetate **8** was isolated in high yield. Another instructive example is the use of 2-cyanoethanol as nucleophilic source. Reaction in MeCN gave the corresponding benzyl ether, 3-[(pentamethylbenzyl)oxy]propanenitrile **9**,[10] while reaction in TFA yielded selectively the benzylamide derivative, 3-oxo-3-[(pentamethylbenzyl)amino]propyl trifluoro acetate **10**.[11]

The more or less efficient benzylic functionalisation of HMB was previously reported to have been carried out by electrochemical[12] and photochemical[13] methods, or by reactions mediated with a metal ions, like Cu(II),[14] Ce(IV),[15] and Tl(III),[16] salts. The simple experimental protocol, in addition to a high level of selectivity, versatility and efficiency of derivatisation mediated by N-F reagents, especially F-TEDA-BF_4, are advantages that make the synthetic method presented a very convenient procedure for direct benzylic functionalisation of HMB. Mechanistic elucidation of this reaction and attempts of to apply it to other alkylbenzene derivatives are in progress, and will be the subject of a future publication.

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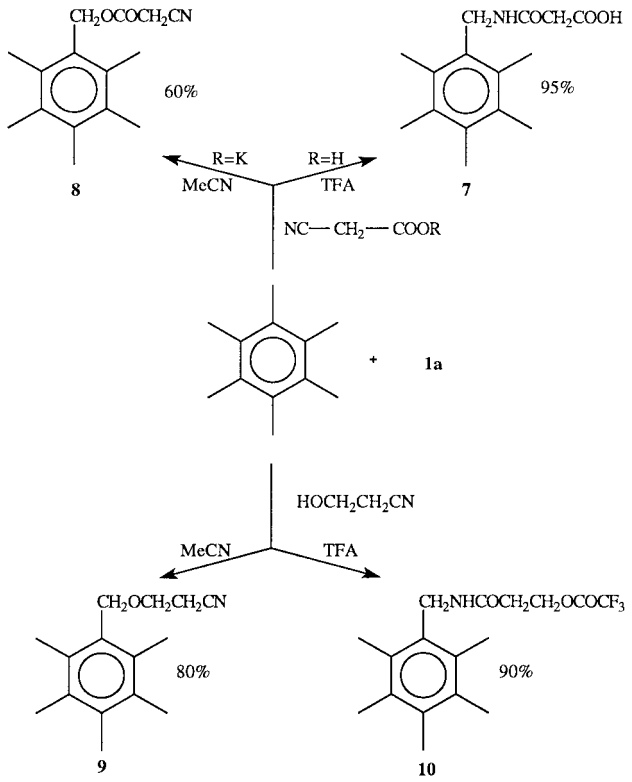

Scheme 2

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(7) 1-Fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**1a**, Selectfluor™ F-TEDA-BF_4) from Apollo, 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**1b**, Accufluor™ NFTh as 50% mixture with Al_2O_3) and N-Fluorobenzenesulfonimide (**1c**, NFSi) from AlliedSignal Inc., N-Fluoro-2,6-dichloropyridinium tetrafluoroborate (**1d**, FP-B800) from Chichibu Onoda Cement Corp., and HMB from Aldrich were used.
Reaction of HMB with N-F regents 1 in the presence of alcohols or TMS-R
To a solution of 5 mmol of HMB in MeCN (50 mL) 25 mmol of corresponding alcohol or TMS derivative (Table) and 5 mmol of N-F reagent **1** were added and the reaction mixture stirred at 55°C until KI starch paper showed the consumption of the reagents. The solvent was removed under reduced presure and the crude reaction mixture dissolved in 100 mL of CH_2Cl_2, insoluble material filtered off, the solution washed with water (2 × 50 mL), dried over anhydrous Na_2SO_4, and the solvent evaporated. The isolated crude reaction mixtures were analysed by ^{1}H NMR and TLC, amounts of products **3a-f** and **5a-b** determined by an internal standard and the pure compounds obtained after flash chromatography over SiO_2. ^{1}H NMR, IR and MS data validated the claimed structures, while the purities of all new compounds were confirmed by elemental analysis.
Reaction of HMB with N-F regents 1 in the presence of cyanides
To a solution of 5 mmol of HMB in TFA (50 mL) 15 mmol of corresponding cyanide and 5 mmol of N-F reagent **1** were added and the reaction mixture stirred at 55°C until KI starch paper showed the consumption of the reagents. The solvent was removed under reduced pressure and the crude reaction mixture dissolved in 100 mL of CH_2Cl_2, insoluble material filtered off, the solution washed with 1% aqueous KOH (50 mL) and water (50 mL), dried over anhydrous Na_2SO_4, and the solvent evaporated to half its volume. The products were precipitated from this solution by n-hexane, filtered off and dried. The precipitated crude products were analysed by ^{1}H NMR and TLC, amounts of compounds **4a-j** determined by internal standard and pure compounds obtained after crystallisation from *n*-hexane/acetone. ^{1}H NMR, IR and MS data validated the claimed structures, while the purities of all new compounds were confirmed by elemental analysis.

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(10) **3-[(Pentamethylbenzyl)oxy]propanenitrile** (**9**):
white crystals; mp 65.7-66.2 °C; ^{1}H NMR: δ = 2.27(s, 6H), 2.35(s, 9H), 2.60(t, J = 6 Hz, 2H), 3.77(t, J = 6 Hz, 2H), 4.70(s, 2H); IR: ν_{CN} = 2220 cm^{-1}, ν_{COC} = 1075 cm^{-1}; MS m/z: 231(M^+, 20%), 216(8), 161(62), 160(100), 147(20), 145(25), 91(25); anal. calcd. for $C_{15}H_{21}NO$: C 77.88, H 9.15, N 6.05; found C 78.29, H 8.92, N 5.96.

(11) **3-Oxo-3-[(pentamethylbenzyl)amino]propyl trifluoro acetate** (**10**):
white crystals; mp 184-185 °C; ^{1}H NMR: δ = 2.30(s, 15H), 2.53(t, J = 5 Hz, 2H), 4.50(t, J = 5 Hz, 2H), 4.60(d, J = 5 Hz, 2H), 5.40(broad s, 1H); ^{19}F NMR: δ = -76.0(s); IR: ν: 3272, 1780, 1620, 1525, 1220, 1150 cm^{-1},; MS m/z: 345(M^+, 24%), 330(13), 161(34), 160(100), 147(25), 145(20); anal. calcd. for $C_{17}H_{22}F_3NO_3$: C 59.12, H 6.42, N 4.06; found C 59.28, H 6.54, N 4.04.

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