Communications to the Editor

Preparation of Tertiary Benzylic Nitriles from Aryl Fluorides

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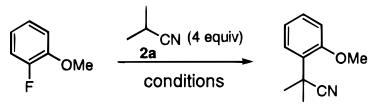
Received September 20, 1999

Nucleophilic aromatic substitution (S_NAr) of aryl halides has been used extensively for the elaboration of complex molecules from simple starting materials.[1,2] Fluoride ion has received much attention as a leaving group and is generally accepted as the best halide in the S_NAr reaction.[3,4] While sulfur, nitrogen, and oxygen nucleophiles have been studied in great detail, there are fewer reports on the use of carbon nucleophiles, such as nitrile anions, in this reaction. For instance, it has been reported that the anion of diphenylacetonitrile reacts with 4-fluoronitrobenzene under phase transfer catalysis,[5] that the anion of phenylacetonitrile reacts with 2-fluorocyanobenzene,[6] and that the enolate of ethyl cyanoacetate adds to either 4-fluoronitrobenzene[7,8] or hexafluorobenzene.[9] However, the addition of a nitrile anion to a fluoroarene not containing another electron withdrawing group has been achieved only when it was first activated as a tricarbonylchromium complex.[10]

Tertiary benzylic nitriles have proven to be not only biologically active compounds, e.g., verapamil and related compounds as slow calcium channel antagonists,[11−15] but also very important synthetic intermediates. For example, they have been used as precursors to bicyclic amidines,[16] lactones,[17] primary amines,[18,19] pyridines,[20] aldehydes,[21,22] carboxylic acids,[23] and esters.[24,25] In general, this class of compounds has been prepared by displacement of an activated benzylic alcohol or halide with cyanide, followed by two successive alkylations. While studying the synthesis of a drug candidate, which featured a tertiary benzylic nitrile, we discovered that the addition of a secondary nitrile anion onto a fluroarene could be achieved under mild conditions.

Table 1. Nucleophilic Aromatic Substitution of **1a** with **2a**



1a **3a**

entry	base (1.5 equiv)	solvent	*T* (°C)	time (h)	yield[a] (%)
1	Cs_2CO_3	THF	75	24	no reaction
2	LDA	THF	RT	<1	decomp
3	*t*-BuOK	THF	70	24	decomp
4	LiHMDS	THF	60	23	3
5	NaHMDS	THF	60	23	49
6	**KHMDS**	**THF**	**60**	**23**	**95**
7	KHMDS/18-C-6	THF	70	45	82
8	**KHMDS**	**toluene**	**60**	**18**	**95**
9	KHMDS	DMSO	75	24	no reaction
10	KHMDS	*i*-Pr_2O	75	24	3
11	KHMDS	NMP	75	24	1

[a] Yields < 5% indicate the conversion observed by HPLC analysis after the time shown. The yields of entries 1, 2, 7, and 8 are isolated yields.

To study the scope and limitation of this reaction, 2-fluoroanisole (**1a**) and isobutyronitrile (**2a**) were chosen as a model system. It was determined that the optimal stoichiometry required 4 equiv of nitrile (**2**) and 1.5 equiv of the base. While the reaction was very slow and would not reach completion at room temperature, it proceeded at an acceptable rate when heated above 60 °C in THF. As shown in Table 1, potassium was the best counterion when a hexamethyldisilazane (HMDS) base was used for the reaction (entries 4−6). The use of $CsCO_3$, LDA, or *t*-BuOK did not provide the desired adduct (entries 1−3), and the addition of 1.5 equiv of 18-crown-6 to KHMDS proved to slow the reaction which never went to completion and provided a lower yield (from 95 to 82%) (entry 7). Toluene proved to be similar to THF (entry 8), while DMSO, *i*-Pr_2O, or NMP turned out to be ineffective for this transformation (entries 9−11).

To establish the scope of the reaction, the nucleophilic aromatic substitution of several fluoroarenes (**1**) with a few secondary nitriles (**2**) was carried out. As indicated in Table 2, the reaction proceeds on electron-rich substrates containing ethers (entries 1−5). Chemoselectivity was achieved as a fluoride reacts preferentially over a chloride, and no product resulting from the

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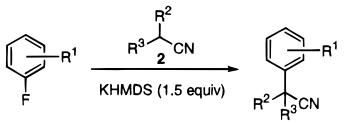
10.1021/ja9933846 CCC: $19.00
Published on Web 01/12/2000

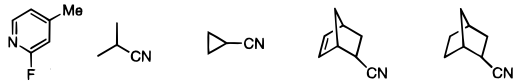
Table 2. S_NAr of Aryl Fluorides with Secondary Nitriles and KHMDS



1 3

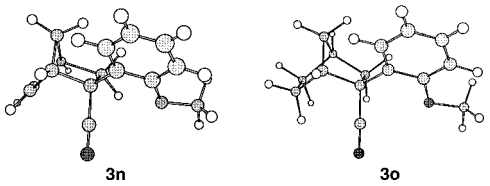
entry	fluoride	nitrile (equiv)	solvent	*T* (°C)	time	yield (%)
1	**1a**, 2-OMe	**2a** (4.0)	toluene	60	18 h	**3a**, 95
2	**1b**, 3-OMe	**2a** (4.1)	toluene	100	3 h	**3b**, 69
3	**1c**, 4-OMe	**2a** (4.0)	THF	60	50 h	**3c**, 66
4	**1d**, 3,5-OMe	**2a** (4.0)	toluene	70	48 h	**3d**, 85
5	**1e**, 3,4-OMe	**2a** (4.0)	THF	80	4 h	**3e**, 28
6	**1f**, 2-Cl	**2a** (4.0)	toluene	60	45 min	**3f**, 77
7	**1g**, 4-Cl	**2a** (4.0)	THF	75	2 h	**3g**, 72
8	**1h**, H	**2a** (4.0)	THF	75	14 h	**3h**, 69
9	**1i**, 3-Me	**2a** (4.0)	THF	75	14 h	**3i**, 71
10	**1j**, 4-CN	**2a** (4.0)	toluene	60	40 min	**3j**, 83
11	**1k**, 4-CF_3	**2a** (3.3)	toluene	60	40 min	**3k**, 94
12	**1l**	**2a** (3.9)	toluene	70	10 min	**3l**, 72
13	**1a**, 2-OMe	**2b** (4.0)	toluene	75	48 h	**3m**, 47
14	**1a**, 2-OMe	**2c** (4.0)	THF	75	24 h	**3n**, 67[a]
15	**1a**, 2-OMe	**2d** (4.0)	THF	75	15 h	**3o**, 70[a]

[a] Provided exclusively the 2*S* isomer (exo aryl).



1l 2a 2b 2c 2d

displacement of the chloride was observed (entries 6 and 7). The reaction can also be carried on fluorobenzene (entry 8) or 3-fluorotoluene (entry 9). In the case of 4-fluorobenzonitrile, displacement of the fluoride was observed exclusively, and addition to the benzonitrile did not occur (entry 10). In the presence of an arene containing an electron-withdrawing group (entries 10 and 11) or a 2-fluoropyridine (entry 12), the reaction was very rapid, as one would normally expect. Furthermore, the anions of cyclopropyl cyanide (**2b**) (entry 13), 5-norbornene-2-carbonitrile (**2c**) (entry 14), and 2-norbornanecarbonitrile (**2d**) (entry 15) all proceeded efficiently in the transformation with 2-fluoroanisole (**1a**). The addition of cyclopropylcyanide (**2b**) is of interest since the product (**3m**) belongs to a class of nitrile which has been used in the generation of imines for cyclopropyl imine rearrangements.[26] Interestingly, the addition of nitriles **2c** and **2d** resulted in the *exo* adduct exclusively.[27] The structures and stereochemistry of products **3n** and **3o** were secured by single-crystal X-ray crystallography.[28] (Figure 1) However, there were limitations on the structures of the nitriles which would undergo addition. The anion must be sufficiently nucleophilic for the aromatic substitution to proceed, since the anion of ethyl cyanoacetate did not undergo reaction. Primary nitriles did not undergo substitution, and reactions using either phenyl acetonitrile or isovaleronitrile with 2-fluoroanisole all led to decomposition. Furthermore, it appears as though the starting material must be a nitrile since the addition of either *N*,*N*-2-trimethylpropionamide, methyl isobutyrate, or 2,4-dimethyl-3-pentanone did not proceed.



3n 3o

Figure 1. Chem3D representation of **3n** and **3o** obtained from X-ray crystal structure.

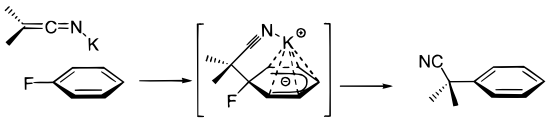


Figure 2. Proposed mechanism for the addition of secondary nitriles to fluoroarenes.

The chemistry described is operationally straightforward. To a solution of the aryl fluoride **1** in THF or toluene (0.3−0.8 M final concentration) were added nitrile **2** (3.3−4.1 equiv) and KHMDS (1.5 equiv). For the reactions in THF solid KHMDS was used, while a 0.5 M toluene solution of base was employed for the reactions in toluene. The reaction mixture was stirred under the conditions indicated in Table 2, after which it was cooled to room temperature, poured into 1 N HCl_{aq}, and extracted with *tert*-butyl methyl ether or toluene. The organic extracts were washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified either by chromatography on silica gel or by recrystallization to afford the desired product **3**. In the case of **3e** (entry 5), preparative HPLC was necessary in order to obtain material of analytically pure quality, which is partially reflected in the low yield reported (28%).

A potential mechanism for the reaction is presented in Figure 2. It is possible that as the addition to the arene proceeds, coordination of the potassium with the developing negative charge occurs. Electron-rich arenes could also facilitate the coordination of the metal prior to addition of the anion. As the product nitrile is generated, cleavage of the nitrogen−potassium bond allows for the generation of a potassium−arene complex, which subsequently eliminates to provide the desired product.

In summary, an efficient method for the addition of secondary nitriles to fluoroarenes has been demonstrated. The reaction is specific to KHMDS but proceeds on a variety of substrates, allowing for a quick entry to a useful class of compounds.

Acknowledgment. We thank Dr. Jon Bordner and Ivan Samardjiev of Pfizer Central Research for the determination of the single-crystal X-ray structure of compounds **3n** and **3o**, Dr. Linda Lohr and Andrew Jensen for the determination of the stereochemistry of the alkylation product of **2c** with benzyl bromide, and Dr. Joel M. Hawkins for several helpful discussions.

Supporting Information Available: Experimental procedures and spectral data for all compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA9933846

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(27) We also demonstrated that the alkylation of nitrile **2c** with benzyl bromide using KHMDS in toluene also proceeds from the *exo* face, and the stereochemistry of the product was confirmed using several NMR experiments.

(28) The author has deposited atomic coordinates for structures **3n** and **3o** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.