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Stereoselective conjugate addition of nitrogen nucleophiles to 3,3,3-trifluoro-1-nitropropene

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Abstract—In order to access 1,2-diamines incorporating perfluorinated groups, the Michael-like addition of nitrogen nucleophiles to 3,3,3-trifluoro-1-nitropropene has been investigated using racemic and optically pure nucleophiles such as amines, amides, oxazolidin(on)es, and thiazolidin(on)es. Complete diastereoselectivity of the addition was achieved with 4-phenylthiazolidine-2-thione.

1. Introduction

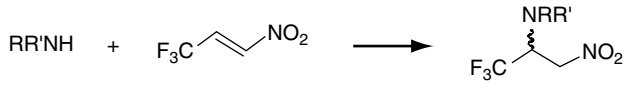
Vicinal diamines have focused the attention of organic chemists for quite a long time (for a review see[1]). 1,2-Diamine functionality is frequently met in biologically active natural and unnatural products.[2] In addition, vicinal diamines are valuable synthetic intermediates that are extensively used in the preparation of nitrogen-containing heterocyclic compounds (piperazines, imidazolines, imidazolidines, etc.[3]) as well as aliphatic amines (amino acids, amino alcohols, etc.[4]). In the field of enantiocontrolled synthesis, they play a large part as chiral auxiliaries and ligands, in stoichiometric as well as in catalytic methodologies.[5–7] Considering the potential of vicinal diamines and the ever increasing attention paid to fluorinated molecules, efforts are required to develop methodologies for the preparation of 1,2-diamines incorporating fluorinated groups. With this aim in view, we decided to investigate the addition of nitrogen nucleophiles to 3,3,3-trifluoro-1-nitropropene. The subsequent reduction of the nitro function would lead to the corresponding primary diamine precursor.

2. Results and discussion

The Michael-like addition of amines to electron-deficient double bonds has been extensively investigated especially the stereoselective version thus providing a useful route to chiral non-racemic amino compounds (for some examples, see[8–13]). However, few other nitrogen nucleophiles have been studied.[14–24] Critically the conjugate addition of nitrogen nucleophiles to fluorinated Michael acceptors has only seldom been reported and is restricted to the addition of some primary amines to α,β-unsaturated carboxylic acid derivatives[25–27] or sulfones,[28–30] and pyrazole and triazoles to *trans*-3,3,3-trifluoro-1-nitropropene.[31]

As a part of a program concerned with the stereoselective addition of nucleophiles to 2-perfluoroalkyl-1-nitroalkenes, we examined the conjugate addition of a series of various nitrogen nucleophiles to *trans*-3,3,3-trifluoro-1-nitropropene (Scheme 1). The results obtained are reported in Table 1.

Though poor stability has been reported for β-aminonitroalkanes,[32,33] it is likely that perfluoroalkyl substituents at the β-position increase the stability of the



Scheme 1.

Keywords: Perfluoroalkyl nitroalkene; Diastereoselective aza-Michael addition; 3,3,3-Trifluoro-1-nitropropene; Oxazolidinone; Oxazolidinethione.
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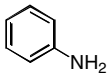
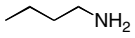
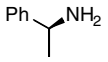
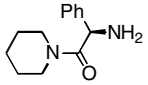
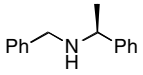
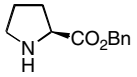
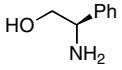
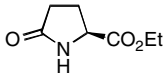
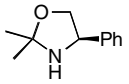
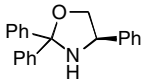
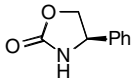
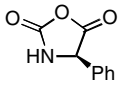
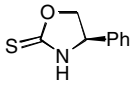
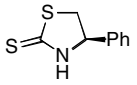
Table 1. Conjugate addition of nitrogen nucleophiles to *trans*-3,3,3-trifluoromethyl-1-nitropropene

Entry	Nucleophile	Method	Yield[a,b] (%)	de[c] (%)
1	NaN_3	A	61	—
2		A	76	—
3		A	60	—
4		A	52	—
5		A	83	20
6		A	89	0
7		A	80	8
8		A	85	50
9		A	94	34
10		B	66	76
11[d]		A	70	14
12		A	0	—
13		B	91	92
14[e]		B	44	40
15		B	40(99[f])	>99.5
16		B	0	—

[a] All of the compounds prepared gave satisfactory ^{1}H, ^{13}C, ^{19}F NMR, and mass spectra.
[b] Isolated compound.
[c] Measured by ^{1}H and ^{19}F NMR in the crude reaction mixture.
[d] N-Alkylated oxazolidine was hydrolyzed during work-up and yield corresponds to isolated amino alcohol.
[e] N-Alkylated oxazolidinedione was hydrolyzed during work-up and yield corresponds to isolated amino acid.
[f] Unreacted starting material was integrally recovered by chromatography.

compounds (entries 2–8). That can be rationalized assuming the β nitrogen atom is less basic when adjacent to an electroattractive perfluorinated group. The difficult coexistence of a basic nitrogen atom and acidic protons α to the nitro function is then wiped out and the naturally easily occurring β-elimination side-reaction is reduced accordingly. The chiral 1-phenyl glycinol bearing two reactive sites only put on evidence N-addition to *trans*-3,3,3-trifluoro-1-nitropropene (entry 9). Amide (entry 10), oxazolidines (entries 11 and 12), oxazolidine-2-one (entry 13), oxazolidine-2,5-dione (entry 14), oxazolidine 2-thione (entry 15), and thiazolidine-2-thione (entry 16) were added to *trans*-3,3,3-trifluoro-1-nitropropene with different scores. Addition of 2,2,4-triphenyl oxazolidine was likely precluded for steric reasons (entry 12) as 2,2-dimethyl homologue compound did react with the Michael acceptor in a good yield (70%).

Sulfur-containing nucleophiles proved the less reactive among those we studied (entries 15 and 16). 4-Phenyl oxazolidine-2-thione slowly reacts with *trans*-3,3,3-trifluoro-1-nitropropene under our standardized conditions and adduct is obtained in 40% yield (entry 15). Non-reacted oxazolidine-2-thione is integrally recovered (60%) after aqueous work-up and silica gel chromatography.

As most of the nucleophiles we have studied are optically active compounds, we took an interest in the diastereoselection of the conjugate addition. Whereas unstrained acyclic 1-phenyl ethylamine and benzyl(1-phenyl ethyl)-amine have been reported to add highly diastereoselectively to many Michael acceptors,[9,10,34–36] with *trans*-3,3,3-trifluoro-1-nitropropene diastereoselectivity was low (8% and 20% de, respectively). Slightly better results were obtained with 1-phenyl glycinol (entry 9, 34% de). More strained cyclic chiral nucleophiles afforded better results except for 2,2-dimethyl 4-phenyl oxazolidine (entry 11, 14% de). 4-Phenyl oxazolidin-2-one has been described to offer total diastereoselectivity upon Michael addition with non-fluorinated nitroalkenes.[21] With a fluorinated substrate, however, the diastereoselectivity of the conjugate addition appears inferior (entry 13, 92% de). A fine tuning of the experimental conditions indicates that full diastereoselectivity could be expected decreasing the temperature below −100 °C. In such conditions however oxazolidinone is not soluble enough to allow synthetically useful conversion.[37] Switching to the less reactive 2-thione compounds series, we could achieve the conjugate addition with a complete diastereoselectivity at −78 °C (entry 15).

3. Experimental

3.1. General information

All reactions were carried out under an inert gas atmosphere (argon), using standard Schlenk techniques. Solvents were dried following standard procedures. *trans*-3,3,3-Trifluoro-1-nitropropene was prepared according to Shechter et al.[38]

3.2. Typical procedures

Method A: trans-3,3,3-Trifluoro-1-nitropropene (185 mg, 1.30 mmol) in THF (5 mL) was added dropwise to

benzylamine (185 μL, 1.69 mmol) in THF (5 mL) at −78 °C. The reaction mixture was stirred for 1 h at −78 °C, saturated aqueous NH_4Cl (5 mL) was added, and the temperature was allowed to rise to room temperature. The mixture was extracted with ether. The organic layer was washed with water, brine, dried over Na_2SO_4, and reduced under vacuum. The crude residue was purified by chromatography over silica gel.

Method B: A 1.6 M solution of *n*-butyllithium in hexane (370 μL, 0.61 mmol) was added dropwise to (*R*)-4-phenyloxazolidin-2-one (100 mg, 0.61 mmol) in anhydrous THF (5 mL) at −78 °C. Deprotonation was allowed to occur for 1 h before *trans*-3,3,3-trifluoro-1-nitropropene (112 mg, 0.79 mmol) in THF (2 mL) was slowly added. The reaction mixture was stirred for 30 min at −78 °C before saturated aqueous NH_4Cl (3 mL) was added. The temperature was allowed to rise to room temperature and work up same as described above.

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