Tetrahedron Letters 50 (2009) 2540–2542

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Functionalized fluoroalkyl heterocycles by 1,3-dipolar cycloadditions with γ-fluoro-α-nitroalkenes

Serena Bigotti [a], Luciana Malpezzi [a], Marco Molteni [a], Andrea Mele [a], Walter Panzeri [a], Matteo Zanda [a,b,*]

[a] C.N.R.—Istituto di Chimica del Riconoscimento Molecolare, and Dipartimento di Chimica, Materiali ed Ingegneria Chimica 'G. Natta' del Politecnico di Milano, via Mancinelli 7, I-20131 Milano, Italy
[b] Institute of Medical Sciences, University of Aberdeen, Foresterhill, Aberdeen AB25 2ZD, Scotland, UK

ARTICLE INFO

Article history:
Received 24 February 2009
Accepted 10 March 2009
Available online 14 March 2009

ABSTRACT

Differently fluorinated γ-fluoro-α-nitroalkenes **1a–d** are effective dipolarophiles in 1,3-dipolar cycloadditions with nitrones and azomethine ylides, respectively, providing fluoroalkyl isoxazolidines **3–12** and pyrrolidines **13–14** in good to excellent yields, with nearly complete regiocontrol and total diastereocontrol in favor of the isomers having *anti*-configuration of the nitro- and fluoroalkyl-substituted carbon centers. The 3,4-cis-cycloadducts were generally produced in higher ratios. In the case of chiral nitrones, such as **2e**, very high diastereocontrol in favor of the endo bicyclic cycloadduct **11** was observed. Interestingly, in most cases the chlorodifluoro nitroalkene **1b** was found to afford the best diastereocontrol.

γ-Fluoro-α-nitroalkenes **1** (Scheme 1) represent a very promising, highly reactive, yet easy-to-handle class of fluorinated building blocks, which have been so far scarcely studied and exploited in the synthesis of functionalized fluoroorganic molecules.[1,3]

Within the frame of a project aimed at the synthesis of fluorinated peptidomimetics via aza-Michael reactions, we became interested in the chemistry of γ-fluoro-α-nitroalkenes **1**,[2] thus we decided to undertake a research program on the synthetic opportunities offered by these interesting fluorinated building blocks in the preparation of fluoroorganic molecules of potential interest in biomedicinal chemistry and materials science.

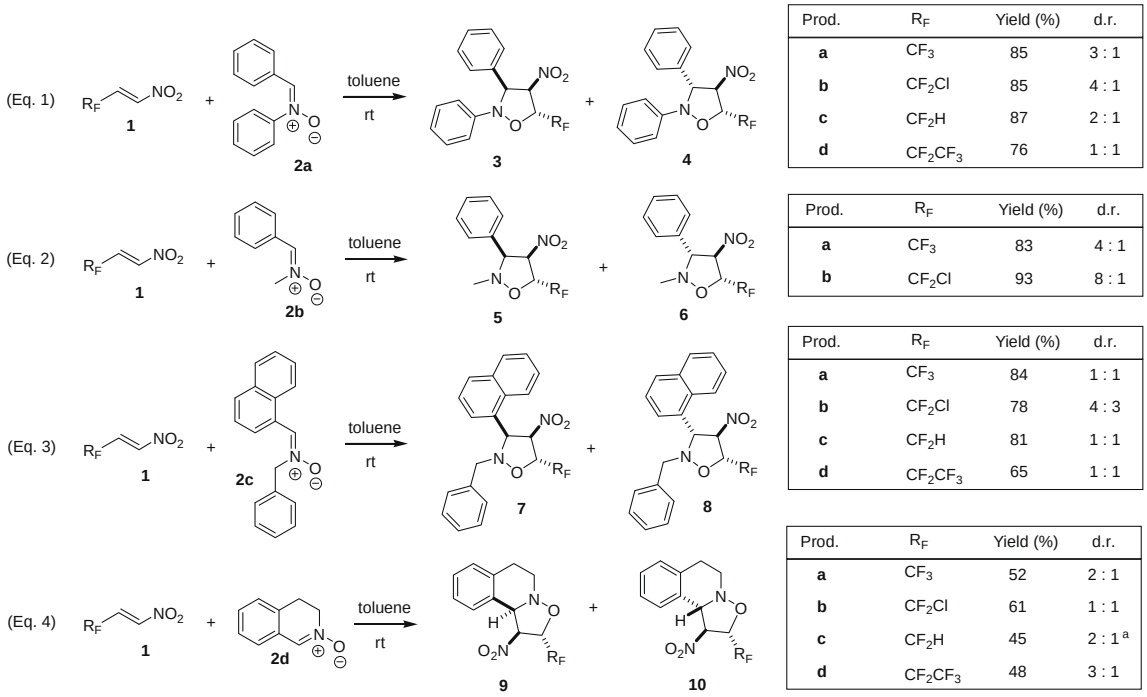
Here we disclose the results of a study on the 1,3-dipolar cycloaddition reaction of nitroalkenes **1a–d** with the 1,3-dipoles **2a–e** (Schemes 1 and 2) and **13** (Scheme 3), which allowed for an efficient entry to an array of highly functionalized nitro- and fluoroalkyl-substituted heterocycles **3–12** (Schemes 1 and 2) and **14** (Scheme 3). The reactivity of compounds **1** is nearly unexplored, as only a handful of papers describing some examples of Diels–Alder,[3] Friedel–Crafts,[4] aza-Michael,[2,5] and Michael reactions,[1b,3,6] are present in the literature. A single example of 1,3-dipolar cycloaddition of **1a** with *C*-phenyl-*N*-methyl nitrone **2b** was also reported (Scheme 1, Eq. 2).[7] The reaction was described to occur with total regiocontrol and 69:31 *endo*-diastereocontrol, affording in quantitative yields *N*-methyl-4-nitro-3-phenyl-5-trifluoromethyl-isoxazolidine **5a**. However, the scope of 1,3-dipolar cycloadditions involving differently fluorinated γ-fluoro-α-nitroalkenes **1** remains virtually unexplored.

The γ-fluoro-α-nitroalkenes **1a–d** were prepared in satisfactory overall yields through the method described in the literature.[1b] According to ^{1}H, ^{13}C, and ^{19}F NMR analysis of **1a–d** in $CDCl_3$, all of them exist exclusively in *E*-form. Since 1,3-dipolar cycloadditions provide a powerful means for the synthesis of a wide range of heterocycles,[8] we decided to investigate the use of **1a–d** for the synthesis of densely functionalized, differently fluorinated heterocycles, which could be valuable molecules in biomedicinal field, as well as intermediates for other bio-important compounds.

C,N-Diphenyl nitrone **2a** (Scheme 2, Eq. 1) reacted overnight with dipolarophiles **1a–d** affording the diastereomeric isoxazolidines **3** and **4** with total regiocontrol and in very good yields.[9] The 4,5-trans stereochemistry of **3, 4** reflects the geometry of the dipolarophiles **1a–d**, and was invariably observed for all of the cycloadducts studied herein. Fair 3,4-cis-diastereocontrol was achieved in favor of products **3a–c**, whereas an equimolar mixture was obtained in the case of the C_2F_5-derivatives **3, 4d**. *C*-Phenyl-*N*-methyl nitrone **2b** (Eq. 2) afforded better stereocontrol in favor of diastereomers 3,4-*cis*-**5** with both dipolarophiles **1a,b**. It is worth noting that the stereoselectivity we recorded for the reaction of **1a** with **2b** is slightly higher than that described in the literature.[7] Surprisingly, no stereocontrol was observed with *C*-naphthyl-*N*-benzyl nitrone **2c** (Scheme 2, Eq. 3), which afforded the isoxazolidines **7** and **8** in good yields and with total regiocontrol, but as a nearly equimolar mixture of diastereomers with all of the nitroalkenes **1a–d**. Isoquinoline-derived nitrone **2d**[10] (Scheme 2, Eq. 4) afforded lower yields of the tricyclic isoxazolidines **9** and **10**, but once again the regiocontrol was excellent. Only in the case of the difluoro-nitroalkene **1c** we could detect, by NMR analysis of the crude reaction mixture, the formation of a regioisomeric cycloadduct (<10% of the mixture).

* Corresponding author. Tel.: +39 0223993084; fax: +39 0223993080.
E-mail address: matteo.zanda@polimi.it (M. Zanda).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.03.059



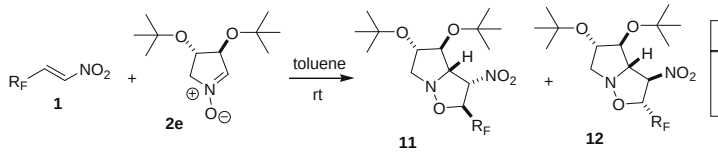
Prod.	R_F	Yield (%)	d.r.
a	CF_3	85	3 : 1
b	CF_2Cl	85	4 : 1
c	CF_2H	87	2 : 1
d	CF_2CF_3	76	1 : 1

Prod.	R_F	Yield (%)	d.r.
a	CF_3	83	4 : 1
b	CF_2Cl	93	8 : 1

Prod.	R_F	Yield (%)	d.r.
a	CF_3	84	1 : 1
b	CF_2Cl	78	4 : 3
c	CF_2H	81	1 : 1
d	CF_2CF_3	65	1 : 1

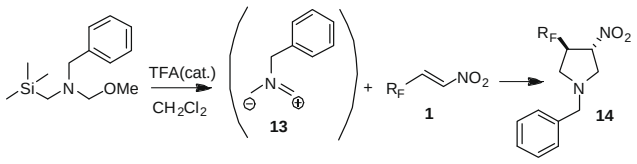
Prod.	R_F	Yield (%)	d.r.
a	CF_3	52	2 : 1
b	CF_2Cl	61	1 : 1
c	CF_2H	45	2 : 1 [a]
d	CF_2CF_3	48	3 : 1

Scheme 1. Diastereomeric ratios determined by ^1H, ^{19}F, and ^{13}C NMR of the crude reaction mixtures. Yields are isolated. [a] A small amount of a regioisomer (less than 10% of the whole product mixture) was observed by NMR analysis of the crude, but we were unable to isolate it in pure form.



Prod.	R_F	Yield (%)	d.r.
a	CF_3	94	28 : 5
b	CF_2Cl	93	11 : 1

Scheme 2. Reactions with chiral nitrone **2e**. Diastereomeric ratios determined by ^1H, ^{19}F, and ^{13}C NMR of the crude reaction mixtures. Yields are isolated. Trace amounts of two other stereoisomers were detected by ^{19}F NMR.



Prod.	R_F	Yield(%)
a	CF_3	75
b	CF_2Cl	88
c	CF_2H	74
d	CF_2CF_3	73

Scheme 3. Reactions with *N*-benzyl azomethine ylide **13**. Yields are isolated.

To further explore the scope of these 1,3-dipolar cycloadditions involving nitroalkenes **1**, the use of the chiral enantiomerically pure nitrone **2e**[11] was also investigated (Scheme 2). Rewardingly, the reaction occurred in high yields and with good diastereocontrol, essentially providing two diastereoisomeric cycloadducts out of four possible (trace amounts of two other stereoisomers were detected by ^{19}F NMR of the crude reaction mixture), with a quite large predominance of **11** over **12**. It is worth noting that the chlorodifluoro nitroalkene **1b** was generally found to afford the highest degrees of stereocontrol, except in the case of the achiral cyclic nitrone **2d**. However, a general trend of diastereocontrol upon changing the fluorinated residue R_F could not be evidenced.

Finally, we investigated the feasibility of azomethine ylides as dipoles. *N*-Benzyl azomethine ylide **13**, generated from *N*-(1-benzyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-amine (Scheme 3),[12] afforded in good to excellent yields the corresponding 3,4-*trans*-*N*-benzyl-pyrrolidines **14a–d**.[13]

The stereochemistries of cycloadducts **7a** (Fig. 1), **7b**, **8a**, **10a**, **10b** (Fig. 2), and **12a** (Fig. 3), were determined by X-ray diffraction.

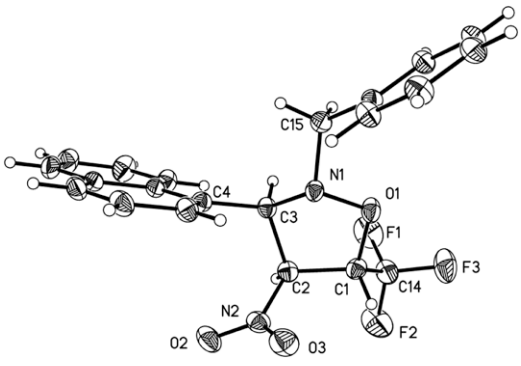


Figure 1. ORTEP view of **7a**.[14]

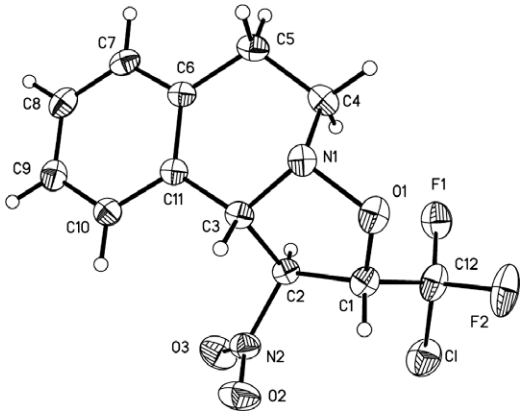


Figure 2. ORTEP view of **10b**.[14]

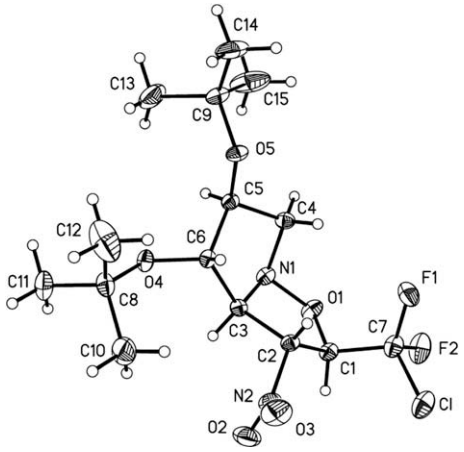


Figure 3. ORTEP view of **12a**.[14]

The stereochemistry of isoxazolidines **3**, **4** was assigned by NMR. For example, **3a** showed $J_{(3-4)}$ = 8.1 Hz and H4{H3} steady state NOE = 12%, indicating that H3 eclipsed with H4 within 3,4-*cis* isoxazolidine, while the corresponding parameters for the same protons in diastereomeric **3b** resulted in 6.4 Hz and 1.9%, respectively, consistent with 3,4-*trans* isoxazolidine showing H3-C3–C4-H4 torsion angle around 120°. The stereochemistry of the other cycloadducts portrayed in Schemes 1 and 2 were assigned on the basis of spectroscopic analogies with the compounds listed above.

Among the tested dipoles, only phenyl nitriloxide failed to react with nitroalkenes **1**, probably owing to its electrophilic nature.

In conclusion we have demonstrated the feasibility of 1,3-dipolar cycloadditions with highly reactive γ-fluoro-α-nitroalkenes **1** for preparing chiral, densely functionalized heterocycles featuring a wide degree of fluorination. The use of the present methodology to access target bioactive compounds is currently under investigation.

Acknowledgments

Politecnico di Milano and C.N.R. are gratefully acknowledged for economic support.

References and notes

1. (a) Schechter, H.; Ley, D. E.; Roberson, E. B., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 4984–4991; (b) Molteni, M.; Consonni, R.; Giovenzana, T.; Malpezzi, L.; Zanda, M. *J. Fluorine Chem.* **2006**, *127*, 901–908.
2. For a review see: (a) Zanda, M. *New J. Chem.* **2004**, *28*, 1401–1411; See also: (b) Molteni, M.; Volonterio, A.; Zanda, M. *Org. Lett.* **2003**, *5*, 3887–3890.
3. Klenz, O.; Evers, R.; Miethchen, R.; Michalik, M. *J. Fluorine Chem.* **1997**, *81*, 205–210.
4. Iwata, S.; Ishiguro, Y.; Utsugi, M.; Mitsuhashi, K.; Tanaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2432–2435.
5. (a) Turconi, J.; Lebeau, L.; Paris, J.-M.; Mioskowski, C. *Tetrahedron* **2006**, *62*, 8109–8114; (b) Korotaev, V. Yu.; Sosnovskikh, V. Ya.; Kutyashev, I. B.; Barkov, A. Yu.; Matochkina, E. G.; Kodess, M. I. *Tetrahedron* **2008**, *64*, 5055–5060.
6. (a) Andrey, O.; Alexakis, A.; Tomassini, A.; Bernardinelli, G. *Adv. Synth. Catal.* **2004**, *346*, 1147–1168; (b) Konno, T.; Tanaka, T.; Miyabe, T.; Morigaki, A.; Ishihara, T. *Tetrahedron Lett.* **2008**, *49*, 2106–2110; (c) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366–6370.
7. Tanaka, K.; Mori, T.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 263–268.
8. Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863–909.
9. A solution of **1** in toluene was added, at room temperature, to a stirred solution of **2a** (1 equiv), in toluene. The resulting solution was stirred overnight at room temperature, then the solvent was removed at reduced pressure, and the crude was purified by flash chromatography.
10. Murahashi, S.-I.; Mitsui, H.; Shiota, T.; Tsuda, T.; Watanabe, S. *J. Org. Chem.* **1990**, *55*, 1736–1744.
11. Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274–5275.
12. Kotian, P. L.; Lin, T.-H.; El-Kattan, Y.; Chand, P. *Org. Process Res. Dev.* **2005**, *9*, 193–197. and references therein.
13. *General procedure*. To a solution of commercial *N*-(1-benzyl)-*N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-amine (1.5 equiv) in dry CH_2Cl_2 at room temperature, a nitroalkene **1** was added. TFA (10% mmol) was then added to the resulting solution; the mixture was stirred at room temperature overnight. The solvent was removed at reduced pressure, and the crude was purified by flash chromatography.
14. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no: CCDC 278588 (**7a**), 278589 (**8a**), 666811 (**7b**), 718614 (**10a**), 666812 (**10b**), 629773 (**12a**). Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK ; fax: +44 1223 336033 ; or e-mail: deposit@ccdc.cam.ac.uk).