JOC*Note*

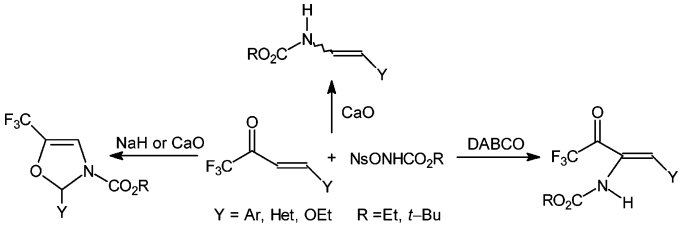
Amination of CF_3-Enones with Nosyloxycarbamates

Daniele Colantoni, Stefania Fioravanti,*
Lucio Pellacani,* and Paolo A. Tardella*

Dipartimento di Chimica, Università degli Studi "La Sapienza", P.le Aldo Moro 2, I-00185 Roma, Italy

lucio.pellacani@uniroma1.it

Received May 3, 2006



CF_3-enones showed a different reactivity in amination reactions with nosyloxycarbamates. 4-Oxazolines or vinyl carbamates were obtained as unique products depending on the nature of double-bond substituents and on the choice of carbamates and bases. Starting from *trans*-trifluoroacetyl olefins carrying a heterocyclic residue or the *p*-methoxyphenyl group on the double bond, a rare loss of CF_3CO was observed when the aminations were performed under heterogeneous conditions using CaO as the base.

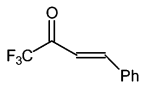
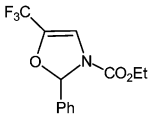
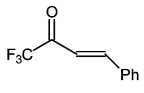
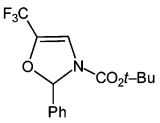
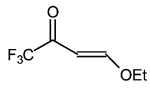
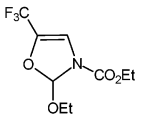
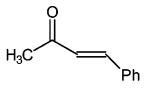
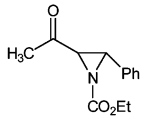
In recent years, fluorocarbon chemistry has attracted an increased interest due to the fundamental effect of fluorine substituents on the structure, bonding and reactivity of organic molecules.[1]

Recently, we reported the electron-withdrawing influence of the trifluoromethyl group on the reactivity of different substituted olefins toward alkyl nosyloxycarbamates ($NsONHCO_2R$) used as aminating agents in the presence of inorganic or organic bases. Simple changes of the olefin backbone and/or the reaction conditions led to different amination products, such as aziridines, β-amino esters, and vinyl carbamates.[2]

Thus, we decided to study the role of the trifluoroacetyl group on the amination reaction outcome of suitable alkenes, by using $NsONHCO_2R$ as aminating agents.

We started from commercial fluorinated products **1**, **2**, and **3** (nonfluorinated analogue of **1**). We tested two different alkyl nosyloxycarbamates, namely $NsONHCO_2Et$ (**4**)[3] and $NsONHCO_2$-*t*-Bu (**5**),[4] as aminating agents using CaO as the inorganic base in CH_2Cl_2. The results are depicted in Table 1.

TABLE 1. Reactivity of Alkyl Nosyloxycarbamates toward Enones 1−3

substrate	aminating agent	molar ratios[a]	time (h)	product	yield[b] (%)
 **1**	**4**	1:3:2	3	 **6**	58
	4	1:2:1[c]	1		51
 **1**	**5**	1:3:2	3	 **7**	52
 **2**	**4**	1:4:3	3	 **8**	56
 **3**	**4**	1:5:3	6	 **9**	52

[a] Substrate/CaO/$NsONHCO_2R$. [b] Yields after chromatographic purification. [c] Performed without solvent.

As shown in Table 1, acyl olefin **3** gives the expected corresponding *trans*-aziridine **9** by an aza-MIRC (Michael-initiated ring closure) reaction,[5] as confirmed by the typical aziridine ^1H NMR signals at δ 3.33 and 3.66. On the contrary, fluorinated olefins **1** and **2** give 5-trifluoromethyl-substituted 2,3-dihydrooxazoles (4-oxazolines) **6**, **7**, and **8** probably through a domino reaction involving a fast rearrangement of unstable 2-trifluoroacetyl aziridines **I** (Scheme 1).[6] The presence of singlet signals at δ 6.67−6.92 in the ^1H NMR of **6**−**8** confirms the structure of the 4-oxazoline ring.

Unfluorinated α,β-enones were already reported by us to give the corresponding acyl aziridines as the only products under

* To whom correspondence should be addressed. Phone: +39 06 49913673. Fax: +39 06 490631.

(1) (a) Smart, B. E. In *The Chemistry of Functional Groups, Supplement D*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1983; pp 603−655. (b) Billard, T. *Chem. Eur. J.* **2006**, *12*, 974−979.

(2) (a) Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2004**, *6*, 197−200. (b) Fioravanti, S.; Colantoni, D.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2005**, *70*, 3296−3298.

(3) Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630−3637.

(4) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synlett* **2004**, 1083−1085.

(5) (a) Little, D. R.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609−2612. (b) Stevens, C. V.; Van Heecke, G.; Barbero, C.; Patora, K.; De Kimpe, N.; Verhe, R. *Synlett* **2002**, 1089−1092. (c) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2003**, 4549−4552. (d) Pohlman, M.; Kazmaier, U.; Lindner, T. *J. Org. Chem.* **2004**, *69*, 6909−6912. (e) Matsumoto, T.; Masu, H.; Yamaguchi, K.; Takeda, K. *Org. Lett.* **2004**, *6*, 4367−4369 and refs therein.

(6) (a) Lown, J. W.; Smalley, R. K.; Dallas, G. *Chem. Commun.* **1968**, 1543−1545. (b) Lown, J. W.; Matsumoto, K. *Can. J. Chem.* **1970**, *48*, 3399−3412. (c) Person, H.; Luanglath, K.; Baudru, M.; Foucaud, A. *Bull. Soc. Chim. Fr.* **1976**, 1989−1992. (d) Freeman, J. P. *Chem. Rev.* **1983**, *83*, 241−261.

10.1021/jo060915h CCC: $33.50 © 2006 American Chemical Society
Published on Web 07/06/2006

SCHEME 1. Domino Reactions Involving Unstable Aziridines I

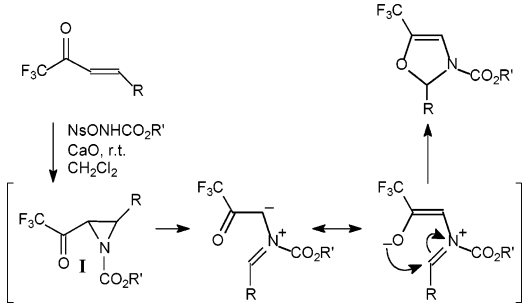
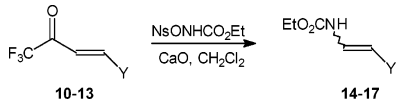


TABLE 2. Reaction of *trans*-Trifluoroacetyl Olefins with $NsONHCO_2Et$ in the Presence of CaO



entry	olefin	Y	molar ratio[a]	time (h)	product (*trans*/*cis*)	yield[b] (%)
1	**10**	2-thienyl	1:3:2	3	**14** (85/15)[c]	65
2	**11**	3-thienyl	1:3:2	3	**15** (91/9)[c]	51
3	**12**	2-furyl	1:3:2	3	**16** (89/11)[c]	45
4	**13**	*p*-MeO-C_6H_4	1:3:2	3	**17** (95/5)[d]	72

[a] Substrate/CaO/$NsONHCO_2Et$. [b] Total yields after chromatographic purification. [c] Calculated by HPLC analyses performed on the crude mixture. [d] Calculated by GC/MS and ^1H NMR analyses performed on the crude mixture. The *cis* isomer was not isolated.

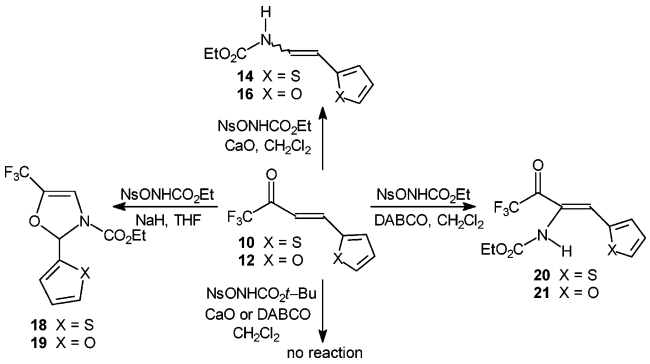
the same amination reaction conditions.[7] On the other hand, we obtained the formation of analogous 4-oxazolines even by direct amination of 2-alkylidene-3-oxo nitriles with nosyloxycarbamates, and we observed the importance of the geminal position of the cyano group with respect to the oxo group on the reaction outcome.[8] The results reported in Table 1 show the same fundamental role for the $COCF_3$ group as the single substituent of the double carbon−carbon bond.

To gain more insights, we decided to synthesize *trans*-trifluoroacetyl olefins carrying different aryl groups on carbon 4. Starting from **2**, we followed literature procedures.[9] The results of amination reactions performed with $NsONHCO_2Et$ in the presence of CaO and CH_2Cl_2 are reported in Table 2.

Unexpectedly, olefins **10**−**13** gave unfluorinated vinyl carbamates. The trifluoroacetyl group seems to behave like a good leaving group, and the *trans* diastereomer was obtained as the major product in all cases. During these reactions, we observed the loss of CF_3CO group. While the stability of $[CF_3CO]^+$ group in gas phase has been reported,[10] to the best of our knowledge reactions involving the loss of CF_3CO are rarely reported in the literature.[11−14]

Aminations of trifluoromethyl enoates by a formal insertion reaction of (ethoxycarbonyl)nitrene (NCO_2Et) to give the corresponding unsaturated amination products were already reported by us.[2b] However, by using CaO as the inorganic base these last products were obtained in low yields, while the expected aziridines were the main amination products. On the contrary, insertion products could be obtained as the main product (aziridine/vinyl carbamate = 7:93) when DABCO was used as the deprotonating reagent. Finally, starting from the same substrates, the aziridines were synthesized as unique products in the presence of NaH.

SCHEME 2. Different Reactivity of *trans*-Trifluoroacetyl Olefins in Amination Reactions



On the basis of our previous experience, we decided to investigate the amination of **10** and **12** by changing both carbamate and base. The results are reported in Scheme 2.

The amination reactions of *trans*-trifluoroacetyl olefins **10** and **12** carried out with **4** under different heterogeneous conditions (NaH/THF) gave **18** or **19** as the only products. On the other hand, the use of homogeneous reaction conditions ($DABCO/CH_2Cl_2$) gave trifluoroacetyl vinyl carbamates **20** (67%) and **21** (49%) by a known C−H insertion reaction of $:NCO_2Et$.[15] The formation of these last compounds supports the involvement of NCO_2Et as the aminating species in the reactions performed on substrates reported in Table 2. As a confirmation of this hypothesis, $NsONHCO_2$-*t*-Bu[16] does not give any amination products when CaO or DABCO was used as base.

Some considerations are possible from analysis of the reported data. At first, as shown in Scheme 1, the choice of inorganic bases was fundamental to obtain *N*,*O*-heterocyclic compounds starting from substrates **10** and **12**. As we reported before,[2b] NaH is known to promote the aza-MIRC reaction, giving heterocyclic compounds. Moreover, the choice of carbamate was crucial to obtain products derived from nitrene attack.

Second, the reaction outcome seems to be influenced also by the nature of the aryl group present on the olefinic bond. In fact, the presence of a heteroaromatic residue and of the *p*-methoxy group on the phenyl ring could favor the positive charge delocalization on the aryl group, making the olefins **10**−

(7) Fioravanti, S.; Pellacani, L.; Tabanella, S.; Tardella, P. A. *Tetrahedron* **1998**, *54*, 14105−14112.

(8) Burini, E.; Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synlett* **2005**, 2673−2675.

(9) (a) Sanin, A. V.; Nenajdenko, V. G.; Smolko, K. I.; Denisenko, D. I.; Balenkova, E. S. *Synthesis* **1998**, 842−846. (b) Andrew, R. J.; Mellor, J. M. *Tetrahedron* **2000**, *56*, 7261−7266.

(10) Cacace, F.; Crestoni, M. E.; Fornarini, S. *J. Phys. Chem.* **1994**, *98*, 1641−1647.

(11) Babaev, E. V.; Bobrovskii, S. I.; Bundel, Yu, G. *Khim. Geterotsikl. Soedin*. **1988**, 1570.

(12) (a) Tolstikov, G. A.; Shul'ts, E. E.; Vafina, G. F. *Zh. Org. Khim.* **1989**, *25*, 2249−2250. (b) Porshnev, Yu. N.; Erikhov, V. I.; Cherkashin, M. I. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1980**, 1145−1147.

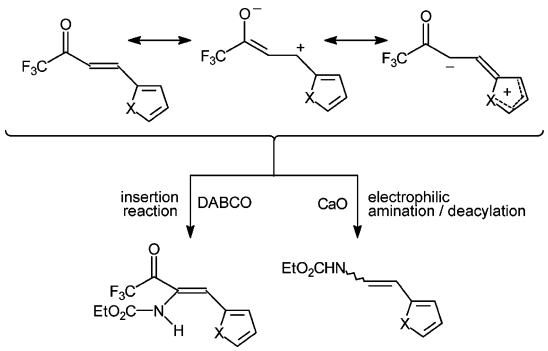
(13) Nishiwaki, T.; Kunishige, N. *J. Chem. Res., Synop.* **1984**, 390−391.

(14) Cordaro, J. G.; Bergman, G. *J. Am. Chem. Soc.* **2004**, *126*, 16912−16929.

(15) Lwowski, W. In *Nitrenes*; Lwowski, W., Ed.; J. Wiley and Sons: New York, 1970.

(16) This carbamate after deprotonation undergoes a very fast Lossen-type transposition, leading to the corresponding isocyanate: (a) Pihuleac J.; Bauer, L. *Synthesis* **1989**, 61−64. (b) Hanessian, S.; Johnstone, S. *J. Org. Chem.* **1999**, *64*, 5896−5903. (c) Fioravanti, S.; Marchetti, F.; Morreale, A.; Pellacani, L.; Tardella P. A. *Org. Lett.* **2003**, *5*, 1019−1021.

SCHEME 3. Different Amination Paths in the Presence of DABCO or CaO



13 worst Michael acceptors and consequently the aza-MIRC reaction does not occur.

Finally, to explain the difference between amination products obtained using CaO and DABCO with $NsONHCO_2Et$, it is possible to propose two different amination paths (Scheme 3).

While under homogeneous conditions it is more probable that trifluoroacetyl vinyl carbamates **20** and **21** were formed by a direct insertion reaction on a vinylic C−H bond, as supported by the formation of a single isomer with plausible *Z* configuration, in the presence of CaO an electrophilic attack on carbon 3 could explain the formation of the *cis*/*trans* mixture of vinyl carbamates **14**−**17**, even through a tetrahedral reaction intermediate, that we were not able to detect in the reaction mixture.

In conclusion, trifluoroacetyl alkenes behave very interestingly in amination reactions with nosyloxycarbamates giving different and even unexpected valuable products. Slight changes in the substrate structures as well as in the always mild reaction conditions allow us to control the reaction outcome.

Experimental Section

General Procedure for Amination Reactions. To a stirred solution of 1 mmol of substrate (**1**−**13**) in CH_2Cl_2 or THF (2 mL/mmol) were added CaO, NaH, or DABCO and $NsONHCO_2Et$ (**4**) or $NsONHCO_2$-*t*-Bu (**5**) portionwise during 1 h and in the molar ratios reported in Table 1 and in Table 2 for the reactions performed in CH_2Cl_2/CaO. The molar ratios (substrate/base/$NsONHCO_2Et$) were 1:2:1.5 with NaH and 1:3:2 with DABCO. The reaction was monitored by TLC or GC, and then, after filtration, the solvent was evaporated under reduced pressure. Products were purified by flash chromatography using hexane/ethyl acetate = 90:10 for compounds **6**−**8**, **18**, and **19**, hexane/ethyl acetate = 80:20 for compounds **9**, and **14**−**17**, and hexane/ethyl acetate = 75:25 for compounds **20** and **21** as eluents, respectively.

Acknowledgment. This research was carried out within the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni", supported by the Italian Ministero dell'Istruzione dell'Università e della Ricerca (MIUR) and by the Università degli Studi di Roma "La Sapienza".

Supporting Information Available: General experimental methods, ^1H and ^{13}C NMR spectra and HRMS-ESI for compounds **6**−**9** and **14**−**21**, and ^{19}F NMR spectra for compounds **6**−**8** and **18**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060915H