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A novel deacylation during the amination of trifluoromethyl β-dicarbonyl compounds

Stefania Fioravanti,* Lucio Pellacani,* Federico Ramadori and Paolo A. Tardella*

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

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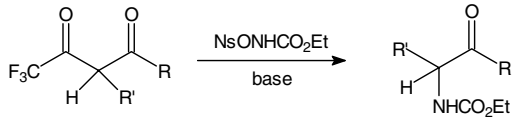
Abstract—Starting from trifluoromethyl β-dicarbonyl compounds, a rare loss of CF_3CO was observed in the amination reactions performed under heterogeneous conditions using $NsONHCO_2Et$ as the aminating agent and CaO or NaH as the base, while corresponding nonfluorinated β-dicarbonyl compounds under analogous conditions give non deacylated aminated compounds. This reaction can facilitate a direct synthesis of N-substituted α-amino esters or α-amino ketones.

The effect of fluorine substituents on the structure, bonding and reactivity of organic molecules is well known and represents the reason for the ongoing interest in the chemistry of such compounds.[1]

During our study on the behavior of CF_3-enones in the base-catalyzed amination reactions with ethyl nosyloxycarbamate ($NsONHCO_2Et$, $Ns = 4\text{-}NO_2C_6H_4SO_2$), a rare loss of CF_3CO was observed, when reactions were performed under heterogeneous conditions using CaO as the base.[2] After the α-elimination reaction on nosyloxycarbamate promoted by CaO,[3] the electrophilic attack of (ethoxycarbonyl)nitrene (NCO_2Et) coupled to a deacylation reaction was proposed to explain the formation of the obtained cis/trans mixture of vinyl carbamates, through an undetected tetrahedral reaction intermediate.

The loss of CF_3CO moiety was unexpected and rarely reported in the literature.[1m,4] Therefore, we studied the outcome of the amination reactions on some trifluoromethyl β-dicarbonyl compounds, comparing also their reactivity with that of nonfluorinated analogues. In fact, some years ago we reported the amination of nonfluorinated β-dicarbonyl compounds with $NsONHCO_2Et$ under heterogeneous conditions (CaO/CH_2Cl_2), yielding the aminated products through a nitrene electrophilic addition.[5]

The amination reactions were performed on the commercially available fluorinated β-dicarbonyl compounds, using an inorganic base to promote the α-elimination reaction on the carbamate. Substrates **1**–**7** were treated with $NsONHCO_2Et$ under heterogeneous conditions (CaO/CH_2Cl_2) at room temperature. The results are reported in Table 1. The amination and deacylation took place in the same reaction vessel, giving directly nonfluorinated α-amino acyl compounds (Scheme 1).[6]



Scheme 1. One pot amination/deacylation of trifluoromethyl β-dicarbonyl compounds.

As shown in Table 1, the loss of trifluoroacetyl group was always observed and no fluorinated products were found in the organic layer. The reaction was exothermic and the development of a gas was observed. The atmosphere was analyzed by a gas chromatograph with an electron capture detector (ECD), and the presence of a fluorine-containing compound was detected.

The behavior of compounds **4** and **5** clearly shows that the deacylation occurs selectively forming the nonfluorinated α-amino ketones **11** and **12**.

Of particular note, starting from commercially available **7**, product **14** was always obtained as a single

Keywords: α-Amino esters; α-Amino ketones; Fluorinated compounds; Deacylation.
* Corresponding authors. Tel.: +39 0649913673; fax: +39 06490631; e-mail: lucio.pellacani@uniroma1.it

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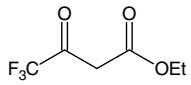
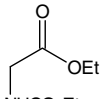
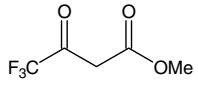
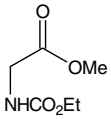
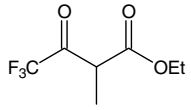
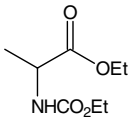
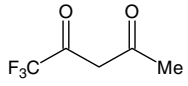
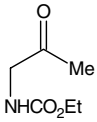
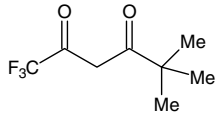
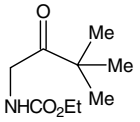
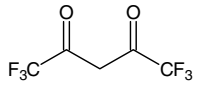
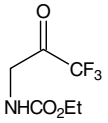
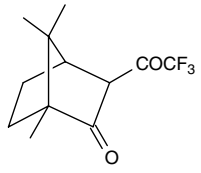
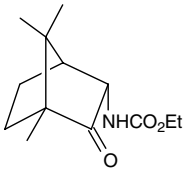
Table 1. Amination reactions with $NsONHCO_2Et$ and CaO in CH_2Cl_2

Substrate	Molar ratios[a]	Time (h)	Product	Yield[b] (%)
 **1**	1:3:2	5	 **8**	51
 **2**	1:3:2	6	 **9**	47
 **3**	1:3:2	5	 **10**	51
 **4**	1:4:3	3	 **11**	53
 **5**	1:4:3	5	 **12**	45
 **6**	1:4:3	3	 **13**	49
 **7**	1:4:3	3	 **14**[c]	61

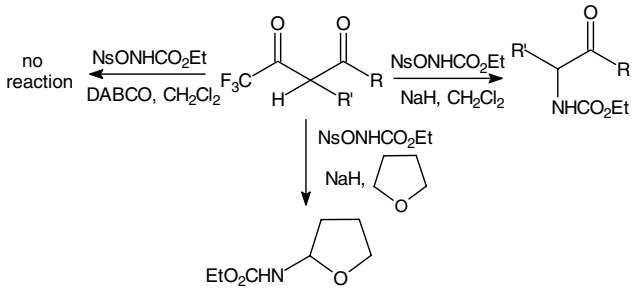
[a] Substrate:CaO:$NsONHCO_2Et$.
[b] After flash chromatography (eluent: hexane–ethyl acetate = 8:2).
[c] Traces (<5%) of the *exo*-isomer were detected by NMR spectra.

stereoisomer with an *endo* configuration of the $NHCO_2Et$ group, as deduced by comparison of its ^1H NMR spectrum with those of *exo*[7] and *endo*[8] strictly related compounds.

In order to gain further insight into the reaction mechanism, we investigated on the possibility that the observed deacylation reaction could occur on fluorinated substrates independently of the amination reaction. Upon treating **1** with CaO in CH_2Cl_2 at room temperature, no reaction was observed after 24 h and the trifluoromethyl β-dicarbonyl compound was quantitatively recovered.

Subsequently, the aminations were performed using NaH or DABCO in CH_2Cl_2, to investigate the effect

of the base on the reaction outcome. While no reaction was observed under homogeneous phase conditions with DABCO, the aminations carried out on **3**, **6**, and **7** by using NaH/CH_2Cl_2 at room temperature or at −40 °C after 12 h led to the same compounds **10**, **13**, and **14**, in 45%, 52%, and 87% yield, respectively (Scheme 2).

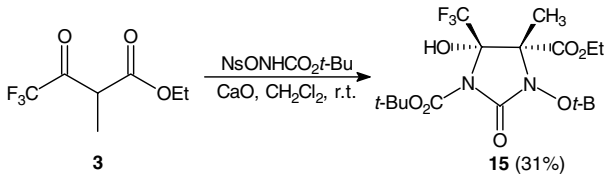


Scheme 2. Amination reaction under different conditions.

In addition, the change of the solvent permitted trapping of the proposed intermediate nitrene. In the amination reactions performed using NaH in anhydrous THF, trifluoromethyl β-dicarbonyl compounds were quantitatively recovered both at room temperature and at −40 °C. The only product observed was that of solvent amination, ethyl tetrahydrofuran-2-ylcarbamate, thereby supporting the proposed intermediacy of (ethoxycarbonyl)nitrene in the reaction of interest.[9]

Finally, the reaction was attempted with *tert*-butyl nosyloxycarbamate ($NsONHCO_2t$-Bu). It is reported that this carbamate after deprotonation does not give the corresponding nitrene but undergoes a very fast Lossen-type rearrangement, leading to the corresponding isocyanate.[10]

Starting from **3**, only the functionalized imidazolidin-2-one **15**[11] was obtained after purification in 31% yield (Scheme 3). As we reported previously for the analogous reactions performed on nonfluorinated β-oxo esters, the formation of the cyclic urea derivative **15** could be rationalized through a multicomponent reaction pathway, involving the aza-anion $NsON^-Boc$ as well as the corresponding *tert*-butoxy isocyanate.[12]



Scheme 3. Synthesis of a functionalized imidazolidin-2-one.

In conclusion, aminations on trifluoromethyl β-dicarbonyl compounds promote an unusual deacylation reaction,[13] probably favored by the basic reaction conditions.[14] As a consequence, starting from trifluoromethyl oxo esters **1** and **3**, N-protected glycine and alanine ethyl esters, respectively, were directly obtained and starting from **6** it was possible to obtain the trifluoromethyl α-amino ketone **13** as useful starting material for the construction of fluorinated peptide analogues, potential inhibitors for a variety of hydrolytic enzymes, including acetylcholinesterase.[15] Interestingly, by monoalkylation reactions of commercially available trifluoromethyl β-dicarbonyl compounds, it will be possible to obtain a direct and simple synthesis of natural or unnatural N-protected α-amino esters and α-amino ketones.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.014.

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6. *General procedure for amination reactions*: To a stirred solution of 1 mmol of substrate in CH_2Cl_2 (2 mL), $NsONHCO_2Et$ and CaO or NaH (in this case anhydrous CH_2Cl_2 was used) were added portionwise at room temperature or at −40 °C, respectively, in the molar ratios reported in Table 1. The reactions were monitored by TLC or GC until completion. When CaO was used, the crude mixtures were diluted with ethyl acetate (10 mL), filtered and the solvents were evaporated under reduced pressure. When NaH was used as base, the crude mixtures were quenched with a saturated NH_4Cl solution and extracted twice with CH_2Cl_2. The collected organic phases were washed with a saturated NaCl solution, dried on Na_2SO_4 and the solvents were evaporated under reduced pressure. The residue was purified by flash chromatography (eluent: hexane–ethyl acetate = 8:2).
Ethyl N-(3,3,3-*trifluoro*-2-*oxopropyl*)*carbamate* (**13**): Colorless oil; IR 3440, 1736 cm^{-1}; ^1H NMR δ 1.22 (t, $J = 7.2$ Hz, 3H), 4.09 (q, $J = 7.2$ Hz, 2H), 4.22 (d, $J = 6.8$ Hz, 2H), 5.80–5.92 (br, 1H); ^{13}C NMR δ 14.6, 42.7, 61.2, 122.2 (q, $^1J_{CF} = 287.2$ Hz), 155.1, 179.9 (q, $^2J_{CF} = 37.4$ Hz); ^{19}F NMR: δ −76.21; ESI-MS (*m*/*z*) 225 ($M+Na^+$).
Ethyl {(1*R*,4*R*)-2-*endo*-4,7,7-*trimethyl*-3-*oxobicyclo*[2.2.1]-*hept*-2-yl}*carbamate* (**14**): Colorless oil; IR 3432, 1749, 1706 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.97 (s, 3H), 0.98 (s, 3H), 1.03 (s, 3H), 1.27 (t, $J = 7.2$ Hz, 3H), 1.52–1.58 (m, 2H), 1.62–1.79 (m, 2H), 2.40–2.45 (m, 1H), 4.06–4.17 (m, 2H), 4.27 (t, $J = 5.4$ Hz, 1H), 4.85 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.4, 14.6, 19.1, 19.3, 19.8, 32.5, 44.0, 48.2, 58.7, 59.4, 61.2, 156.5, 217.0; GC–MS (*m*/*z*) 239 (M^+ 0.5), 128 (100), 122 (20), 56 (27), 41 (9); ESI-MS (*m*/*z*) 262 ($M+Na^+$).
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11. The same procedure reported for the reactions with $NsONHCO_2Et$ was followed in the amination performed with $NsONHCO_2t$-Bu and CaO.
1-*tert-Butyl* 4-*ethyl* (4*R**,5*S**)-3-*tert-butoxy*-5-*hydroxy*-4-*methyl*-2-*oxo*-5-(*trifluoromethyl*)*imidazolidine*-1,4-*dicarboxylate* (**15**): Colorless crystals, mp 131–133 °C ($CHCl_3$–pentane); IR 3302, 1808, 1756, 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $J = 7.2$ Hz, 3H), 1.29 (s, 9H), 1.58 (s, 9H), 1.65 (s, 3H), 4.26 (ABX, $J_{AB} = 10.8$ Hz, $J_{AX,BX} = 7.2$ Hz, 2H), 7.14 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 15.3, 28.0, 62.5, 71.6, 83.1, 85.9 (q, $^2J_{CF} = 32.9$ Hz), 86.3, 122.6 (q, $^1J_{CF} = 290.3$ Hz), 152.2, 155.3, 166.9; ^{19}F NMR (282.2 MHz, $CDCl_3$, C_6F_6 as internal standard): δ −79.96; ESI-MS (*m*/*z*) 451 ($M+Na^+$).
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