Synthesis of N-Protected Cyano Aziridines

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Abstract: A concise and inexpensive route to 2-cyano aziridine-2-carboxylates and 2,2-dicyano aziridines is reported by reaction of the easily obtainable corresponding α,β-unsaturated nitriles with sulfonyloxycarbamates in the presence of calcium oxide.

Key words: aminations, Michael additions, nitriles, carbamates, ring closure

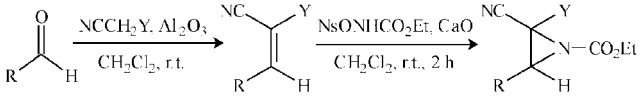
2-Cyanoaziridine and related compounds such as imexon and ciamexon have shown carcinostatic activity and low toxicity.[1] The studies seem to assign a very important role of the cyano group for the pharmacological activity.[2] The patent literature contains claims to numerous 2-cyano aziridines N-substituted with esters of carboxylic acids, acylcarboxamides, sulfonylcarboxamides, and phosphorylcarboxamides.[3] Some of these compounds have alkyl or phenyl substituents at position 3, and others have the cyano group replaced by a carboxamide or a carboxylic ester function. Recently a multi-step synthesis of N-substituted 2-cyano aziridine-2-carboxylates has been reported.[4]

The aziridine ring[5] itself is known as a versatile building block for the synthesis of nitrogen-containing compounds and of modified amino acids or other biologically active compounds. The aziridine ring substituents can also play an important role in the medical potentialities of these compounds, modifying their chemical reactivity and influencing their toxicity, lipophilicity, and alkylating power.[6] Aziridine-2-carboxylates have been used in the construction of peptidomimetics and tested as different enzyme inhibitors.[7]

We are currently engaged in the study of simple and efficient aziridination of EWG-substituted olefins.[8] Aiming to validate a straightforward and general synthetic method leading to substituted 2-cyano aziridine-2-carboxylates and 2,2-dicyano aziridines, we decided to investigate the direct conversion of (*E*)-2-cyano acrylates **1a**–**j** and α,β-unsaturated 1,1-dinitriles **1k**–**n** into the target products by aza-Michael addition of N-protected *O*-sulfonyl hydroxylamine derivatives.

The reaction results are shown in Table 1. Starting from different aldehydes and ethyl cyanoacetate or malononitrile through Knoevenagel condensation,[9] the addition of ethyl nosyloxycarbamate ($NsONHCO_2Et$, Ns = 4-nitrophenylsulfonyl)[10] and calcium oxide gave the full conversion of the intermediate alkenes into the desired 2-cyano aziridines **2a**–**n** in good yields and with high purity, after only a fast filtration of crude mixtures through plugs of silica gel.[11]

Table 1 Aziridination of α,β-Unsaturated Nitriles



1a-j Y = CO_2Et
1k-n Y = CN

2a-n

Entry	R	2	Molar ratio[a]	Yield (%)[b]
1	Et	**a**	1:2:1	93
2	Pentyl	**b**	1:2:1	94
3	Me	**c**	1:2:1	90
4	Bu	**d**	1:2:1	93
5	Bn	**e**	1:2:1	89
6	*i*-Bu	**f**	1:4:2[c]	82
7	*i*-Pr	**g**	1:6:3[c]	76
8	Neopentyl	**h**	1:6:3[c]	74
9	*t*-Bu	**i**	1:10:8[d]	62
10	Cy	**j**	1:10:8[d]	68
11	Et	**k**	1:2:1	91
12	Pentyl	**l**	1:2:1	95
13	Me	**m**	1:2:1	98
14	Bu	**n**	1:2:1	92

[a] Substrate:CaO:$NsONHCO_2Et$.
[b] After purification.
[c] Stirred for 6 h.
[d] Stirred overnight.

The reactivity was found to be influenced by steric hindrance of the R substituents on acrylates. Usually, the reaction reached completion in two hours using equimolar amounts of substrate and carbamate and a two-fold excess of the inorganic base. As expected, increasing the steric hindrance, longer times and higher molar ratios were required (entries 6–10), nevertheless a high stereoselectivity was observed in all pertinent cases (entries 1–10).

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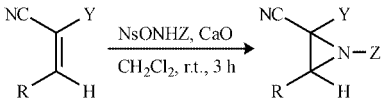
It is noteworthy that high chemoselectivity in the amination reaction is induced by CaO even in the presence of the cyano group, that is reported to give also the corresponding oxadiazoles under homogeneous reaction conditions.[12]

Aziridines were also obtained starting from α,β-unsaturated 1,1-dinitriles **1k**–**n** (entries 11–14), showing no differences in reactivity and yields.

In order to extend the study of the sulfonyl-activated hydroxycarbamate reactivity, reagents with Cbz,[13] Boc,[14] or Fmoc[15] groups rather than ethoxycarbonyl group were tested in the reactions on some α,β-unsaturated nitriles **1**.

Table 2 Aziridination of α,β-Unsaturated Nitriles Using Different Sulfonyloxycarbamates



1a,b Y = CO_2Et
1k,l Y = CN

3a,b
3k,l

Entry	Substrate[a]	Z	Yield (%)[b]
1	**1a**	Cbz	86
2	**1a**	Boc	81
3	**1a**	Fmoc	92
4	**1k**	Boc	82
5	**1b**	Cbz	81
6	**1b**	Boc	78
7	**1b**	Fmoc	96
8	**1l**	Boc	80

[a] Substrate:CaO:NsONHZ = 1:2:1 (molar ratio).
[b] After purification.

As shown in Table 2, different N-protected 2-cyano aziridine-2-carboxylates and 2,2-dicyano aziridines were obtained in high yields and with complete stereoselectivity (entries 1–3 and 5–7).

In summary, a general procedure for the synthesis of highly functionalized aziridines was reported. Despite their potential use and application, only few examples of general synthetic methods of cyano aziridines are reported in the literature.[16] This concise and inexpensive route may be considered as an efficient protocol for a parallel synthesis of a large number of different cyano aziridines.

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References

(1) (a) Bicker, U. W. In *Immune Modulation Agents and their Mechanisms*; Fenical, R. G.; Chirigos, M. A., Eds.; Marcel Dekker: New York and Basel, **1984**, 447. (b) Iyengar, B. S.; Dorr, R. T.; Alberts, D. S.; Hersh, E. M.; Salmon, S. E.; Remers, W. A. *J. Med. Chem.* **1999**, *42*, 510.
(2) Iyengar, B. S.; Dorr, R. T.; Remers, W. A. *J. Med. Chem.* **2004**, *47*, 218.
(3) (a) Remers, W.; Iyengar, B. US 6476236, **2002**; *Chem. Abstr*. **2002**, *137*, 337772. (b) Lopez-Berestein, G.; Remers, W. A.; Hersh, E. M. PCT Int. Appl. 2002041871, **2002**; *Chem. Abstr*. **2002**, *137*, 10970. (c) Kitagawa, S.; Minafuji, M.; Yokoi, T. Jpn. Kokai Tokkyo Koho JP 61140561, **1986**; *Chem. Abstr*. **1987**, *106*, 50009. (d) Bosies, E.; Berger, H.; Kampe, W.; Bicker, U.; Grafe, A. US 4410532, **1983**; *Chem. Abstr*. **1984**, *100*, 68151. (e) Berger, H.; Gall, R.; Kampe, W.; Bicker, U.; Kuhn, R. Ger. Offen DE 2948832, **1981**; *Chem. Abstr*. **1981**, *95*, 115257.
(4) Boukhris, S.; Souizi, A. *Tetrahedron Lett.* **2003**, *44*, 3259.
(5) (a) Tanner, D. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 599. (b) Li, A.-H.; Dai, L.-X.; Aggarwal, V. K. *Chem. Rev*. **1997**, *97*, 2341. (c) Stamm, H. *J. Prakt. Chem.* **1999**, *4*, 319. (d) Atkinson, R. S. *Tetrahedron* **1999**, *55*, 1519. (e) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (f) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247.
(6) (a) Goodridge, T. H.; Huntress, W. T.; Bratzell, R. P. *Cancer Chemother. Rep.* **1963**, *26*, 341. (b) Dermer, O. C.; Ham, G. E. *Ethyleneimine and other Aziridines*; Academic Press: New York and London, **1969**, 425.
(7) (a) Dauban, P.; Dodd, R. H. *Tetrahedron Lett.* **1998**, *39*, 5739. (b) Schirmeister, T.; Peric, M. *Bioorg. Med. Chem.* **2000**, *8*, 1281.
(8) (a) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Synthesis* **2001**, 1975. (b) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **2002**, *67*, 4972. (c) Colantoni, D.; Fioravanti, S.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2004**, *6*, 197.
(9) Texier-Boullet, F.; Foucaud, A. *Tetrahedron Lett.* **1982**, *23*, 4927.
(10) Lwowski, W.; Maricich, T. J. *J. Am. Chem. Soc.* **1965**, *87*, 3630.
(11) **Typical Experimental Procedure**: All compounds were synthesized with a Carousel Reaction Station from Radleys Discovery Technologies (UK). The synthesis involved the following sequential steps. To the stirred solutions of 2.0 mmol of ethyl cyanoacetate or malononitrile in CH_2Cl_2, 2.4 mmol of aldehyde and 1.0 g of basic Al_2O_3 were added. Upon completion, reaction mixtures were filtered. To the so obtained unsaturated nitriles in CH_2Cl_2, CaO and nosyloxycarbamates were added in the amounts reported in Table 1 and Table 2. After completion (TLC), the crude aziridines were filtered through plugs filled with silica gel using a 9:1 hexane/EtOAc mixture and obtained as pale yellow oils after solvent removal. Selected spectral data of new compounds. Compound **2a**: IR (CCl_4): 2253, 1761, 1731 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H), 1.34 (t, *J* = 7.2 Hz, 3 H), 1.68–1.82 (m, 2 H), 3.08 (t, *J* = 6.6 Hz, 1 H), 4.09–4.23 (m, 2 H), 4.23–4.45 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.4, 14.0, 14.2, 23.3, 38.6, 51.3, 63.4, 64.1, 113.3, 157.2, 162.6. GC/MS: *m/z* (%) = 240 (9) [M^+], 114 (24), 95 (46), 94 (12), 68 (100), 67 (10). HRMS (ES Q-TOF) calcd for $C_{11}H_{17}N_2O_4$ $(M + H)^+$: 241.1188; found: 241.1200. Compound **2k**: IR (CCl_4): 2253, 1756 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 7.3 Hz, 3 H), 1.35 (t, *J* = 7.3 Hz, 3 H), 1.66–1.89 (m, 2 H), 3.19 (t, *J* = 6.6 Hz, 1 H), 4.22–4.48 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 9.9, 14.0,

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23.1, 25.0, 52.4, 64.9, 110.3, 110.8, 156.2. GC/MS: *m/z* (%) = 193 (3) [M^+], 121 (21), 94 (100), 93 (53), 83 (10), 68 (15), 67 (75), 66 (38), 65 (10), 56 (23), 54 (11). HRMS (ES Q-TOF) calcd for $C_9H_{12}N_3O_2$ $(M + H)^+$: 194.0930; found: 194.0927.

(12) Lwowski, W. *In Nitrenes*; Lwowski, W., Ed.; John Wiley and Sons: New York, **1970**, Chap. 6.

(13) Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Eur. J. Org. Chem.* **2003**, 4549.

(14) (a) Banks, M. R.; Cadogan, J. I. G.; Gosney, I.; Hodgson, P. K. G.; Langridge-Smith, P. R. R.; Millar, J. R. A.; Taylor, A. T. *J. Chem. Soc., Chem. Commun.* **1995**, 885. (b) N-Boc-protected *O*-sulfonyl hydroxylamine showed no predictable reactivity, see ref.[13] and: Fioravanti, S.; Marchetti, F.; Morreale, A.; Pellacani, L.; Tardella, P. A. *Org. Lett.* **2003**, *5*, 1019.

(15) 9-Fluorenylmethyl nosyloxycarbamate (NsONHFmoc) was synthesized in 80% yield, starting from commercial 9-fluorenylmethyl *N*-hydroxycarbamate (HONHFmoc) and nosyl chloride following the standard procedure, see ref.[10]

(16) (a) De Kimpe, N.; Sulmon, P.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1983**, *48*, 4320. (b) Charrier, J.; Foucaud, A.; Person, H.; Loukakou, E. *J. Org. Chem.* **1983**, *48*, 481.

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