Efficient Synthesis of 4-Cyano 2,3-Dihydrooxazoles by Direct Amination of 2-Alkylidene 3-Oxo Nitriles

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Abstract: The addition of N-protected *O*-sulfonyl hydroxylamine derivatives on 2-alkylidene 3-oxo nitriles gives 2,5-disubstituted 4-cyano 2,3-dihydrooxazoles (4-oxazolines) by a practical and efficient synthetic procedure under very mild conditions in high yields. Likely, the formation of *N*,*O*-heterocycles proceeds through a domino reaction involving a fast rearrangement of unstable 2-acyl 2-cyano aziridines.

Key words: Michael additions, cyclizations, domino reactions, 2-acyl aziridines, heterocycles

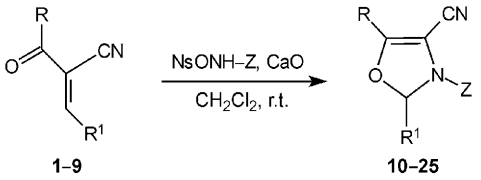
General synthetic approaches to N- and/or O-heterocyclic structures involve often cycloaddition reactions, ring expansion or contraction, and intramolecular cyclization reactions.[1]

We reported the formation of functionalized aziridines by an aza-MIRC (Michael-initiated ring-closure) reaction given by N-protected *O*-sulfonyl hydroxylamine derivatives in the presence of bases on variously substituted olefins.[2] Recently, we applied this aziridination reaction to prepare a large number of 2-cyano aziridines, obtained in high yields and purities from different 2-cyano acrylates or α,β-unsaturated 1,1-dinitriles.[3]

Continuing our studies, we addressed our attention to the reactivity of 2-alkylidene 3-oxo nitriles in order to consider the influence of the oxo group on these amination reactions and on the stability of the corresponding 2-acyl aziridines. In fact, these compounds can show interesting chemical behaviors like thermal rearrangement leading to important synthetic intermediates.[4]

Alkenes **1**–**9** were synthesized through Knoevenagel condensation reactions[3,5] catalyzed by alumina from different aldehydes and 3-oxo nitriles. After filtration, compounds **1**–**6** (purities up to 95%, determined by NMR and HPLC analyses) were used without further purification, while compounds **7**–**9** required chromatographic purification due to the presence of unreacted excesses of aldehydes in the crude reaction mixtures.

Amination reactions were performed using different nosyloxycarbamates[3] (NsONH–Z, Ns = 4-nitrophenylsulfonyl; Z = CO_2Et, Boc, Cbz) in the presence of calcium oxide at room temperature and led to the unexpected formation of 2,5-disubstituted 4-cyano 2,3-dihydrooxazoles



Scheme 1 Amination of 2-alkylidene 3-oxo nitriles

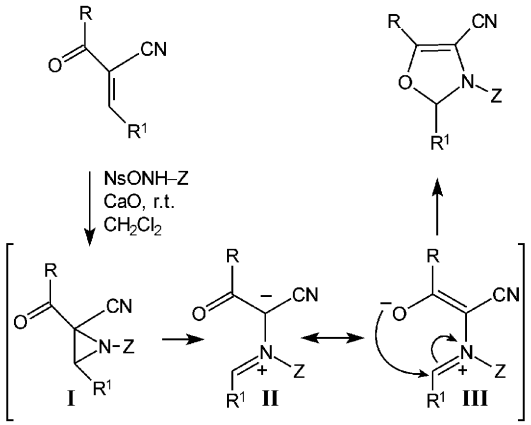
10–**25** (Scheme 1) with high purity, as shown by NMR spectra.[6]

Reaction conditions and yields are reported in Table 1.

The presence of bulky groups like neopentyl (entries 6–8) or *tert*-butyl (entry 14) as well as the presence of a phenyl group (entries 15–16) on the double bond of starting alkenes did not influence the reaction outcomes, even by changing the residue of the acyl moiety.

Although the Z group of the sulfonyloxycarbamates was found to strongly characterize the pathway of these reaction leading often to different results,[7] functionalized 2,3-dihydrooxazoles were always obtained as the only products by using different nosyloxycarbamates.

N,*O*-Heterocycles could be formed by a domino reaction involving a fast rearrangement of the unstable 2-acyl 2-cyano aziridines **I**.[8] The last ones led to the substituted 2,3-dihydrooxazoles under mild conditions, reasonably through the enolate mesomeric forms **III** of the intermediate azomethine ylides **II** (Scheme 2).[9]



Scheme 2 Possible pathway for the synthesis of substituted 2,3-dihydrooxazoles

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Table 1 Synthesis of 2,5-Disubstituted 4-Cyano 2,3-Dihydrooxazoles

Entry	Substrate[a]	R	R^1	Z	Product	Molar ratios[b]	Time (h)	Yield (%)[c]
1	**1**	Ph	Et	CO_2Et	**10**	1:2:2	2	80
2	**1**	Ph	Et	Cbz	**11**	1:2:2	2	62
3	**2**	*t*-Bu	Et	CO_2Et	**12**	1:3:3	2	75
4	**2**	*t*-Bu	Et	Cbz	**13**	1:2:1	2	81
5	**2**	*t*-Bu	Et	Boc	**14**	1:8:4	24	77
6	**3**	Ph	Neopentyl	CO_2Et	**15**	1:3:2	3	61
7	**4**	*t*-Bu	Neopentyl	CO_2Et	**16**	1:2:1	4	86
8	**4**	*t*-Bu	Neopentyl	Cbz	**17**	1:2:1	4	91
9	**5**	Ph	*i*-Bu	CO_2Et	**18**	1:2:2	20	88
10	**6**	*t*-Bu	*i*-Bu	CO_2Et	**19**	1:2:2	6	72
11	**6**	*t*-Bu	*i*-Bu	Boc	**20**	1:2:2	2	93
12	**7**	Ph	Pentyl	CO_2Et	**21**	1:3:2	2	70
13	**7**	Ph	Pentyl	Boc	**22**	1:3:2	2	77
14	**8**	*t*-Bu	*t*-Bu	CO_2Et	**23**	1:2:2	24	55
15	**9**	Ph	Ph	CO_2Et	**24**	1:3:2	8	90
16	**9**	Ph	Ph	Boc	**25**	1:3:2	8	92

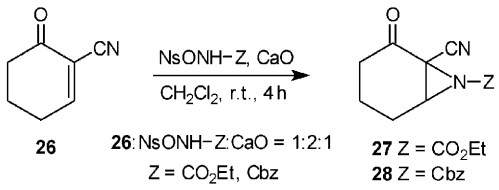
[a] All alkenes were obtained as pure *E* isomers, but **3** (entry 6) as an *E*/*Z* = 2:1 mixture (NMR).
[b] Substrate:CaO:NsONH–Z.
[c] Isolated yield. The structure of all compounds was confirmed by ^{1}H NMR, ^{13}C NMR and HRMS analyses.

It has been reported that 2,3-dihydrooxazoles can be obtained by thermal or photochemical C–C bond cleavage of 2-acyl aziridines through the corresponding azomethine ylides.[10] These last 1,3-dipolar reactive intermediates are commonly employed to synthesize heterocyclic compounds,[11] but their isolation is often difficult and secondary reactions can afford different products like pyrroles, piperazines or exactly 2,3-dihydrooxazoles.[9]

According to Scheme 2, the presence of the intermediate aziridine **I** was detected by ^{1}H NMR spectra performed on the crude amination mixture of alkene **2** with NsONHCbz (Table 1, entry 4).[12] While standing at room temperature, the aziridine disappeared spontaneously and quantitatively gave the corresponding 2,3-dihydrooxazole **13**.

Finally, cyclic 2-alkylidene 3-oxo nitrile **26** yielded stable bicyclic aziridines **27** (yield 75%) and **28** (yield 62%), as expected (Scheme 3), supporting the proposed pathway.

In the reactions reported herein, a different and important role could be played from the geminal position of the cyano and the oxo groups,[13] allowing a practical and efficient synthetic approach to diverse *N*,*O*-heterocycles under mild conditions. These compounds are reported to have synthetic relevance as a route to stabilized azomethine ylides[14] and more recently they have also found



Scheme 3 Synthesis of bicyclic aziridines

applications in different fields.[15] Therefore, the development of new methods for preparation of functionalized 2,3-dihydrooxazoles (4-oxazolines) is a continuous attracting feature for the synthetic organic chemists.[16]

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(6) **Typical Experimental Procedure.**
All compounds were synthesized with a Carousel Reaction Station from Radleys Discovery Technologies (U.K.). To the obtained 2-alkylidene 3-oxo nitriles in CH_2Cl_2, CaO and nosyloxycarbamates were added in the amounts reported in Table 1. After completion (TLC and GC analyses), the crude reaction mixtures were filtered through plugs of silica gel using a 9:1 hexane–EtOAc mixture and the 2,5-disubstituted 4-cyano 2,3-dihydrooxazoles were obtained after solvent removal.
Selected spectral data of new compounds.
Compound **13**: yellow oil. IR (CCl_4): 2223, 1714, 1630 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.2 Hz, 3 H), 1.28 (s, 9 H), 1.67–1.78 (m, 2 H), 5.23 (s, 2 H), 5.97 (t, *J* = 5.4 Hz, 1 H), 7.30–7.48 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.7, 23.7, 27.8, 40.9, 69.2, 91.0, 95.3, 116.4, 128.1, 128.3, 128.8, 135.1, 152.1, 157.9. GCMS: *m*/*z* (%) = 314 (2) [M^+], 179 (11), 137 (27), 91 (100), 57 (15). HRMS (ES Q-TOF): *m*/*z* calcd for $C_{18}H_{23}N_2O_3$ [M + H]$^+$: 315.1709; found: 315.1601.
Compound **18**: yellow oil. IR (CCl_4): 2218, 1717, 1645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.6 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.36 (t, *J* = 7.2 Hz, 3 H), 1.68–1.74 (m, 2 H), 1.87–1.92 (m, 1 H), 4.29 (q, *J* = 7.2 Hz, 2 H), 6.24 (dd, *J* = 6.6 Hz, 1 H), 7.40–7.53 (m, 3 H), 7.84–7.87 (m, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 22.4, 22.7, 23.4, 42.8, 63.0, 90.9, 93.7, 114.7, 125.9, 126.3, 128.6, 128.7, 131.3, 152.7, 156.3. GCMS: *m*/*z* (%) = 300(7) [M^+], 227 (12), 171 (53), 145 (14), 105 (100), 77 (32). HRMS (ES Q-TOF): *m*/*z* calcd for $C_{17}H_{21}N_2O_3$ [M + H]$^+$: 301.1552; found: 301.1546.
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(8) The formation of the unstable 2,3-dihydroisoxazole (4-isoxazoline) (**IV**, Figure 1), as the precursor of aziridine **I** shown in the Scheme 2, is not supported by any experimental evidence. For a recent example of 2,3-dihydroisoxazoles as synthons for 2-acyl aziridines see: Ishikawa, T.; Kudoh, T.; Yoshida, J.; Yasuhara, A.; Manabe, S.; Saito, S. *Org. Lett.* **2002**, *4*, 1907.

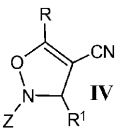

Figure 1

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(12) With respect to **13**,[6] the ^1H NMR spectrum of the crude mixture shows additional frequencies at δ = 1.12 (t, *J* = 7.2 Hz, 3 H), 1.31 (s, 9 H), 1.83–1.98 (m, 2 H), 2.90 (t, *J* = 6.6 Hz, 1 H), 5.08–5.20 (m, 2 H). In particular the signal at δ = 2.90 is typical of an aziridine proton.
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