

Tandem Reactions of 1,2,4-Oxadiazoles
with Allylamines

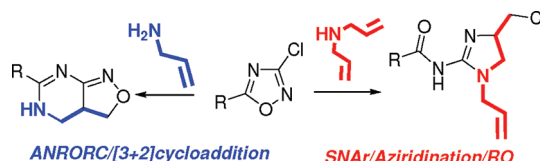
Antonio Palumbo Piccionello,* Andrea Pace, and Silvestre Buscemi

Dipartimento di Scienze e Tecnologie Molecolari e Biomolecolari (STEMBIO), Sez.
Chimica Organica, Università degli Studi di Palermo, Viale delle Scienze, Parco
d'Orleans II, Ed. 17, I-90128 Palermo, Italy

apalumbo@unipa.it

Received July 14, 2011

ABSTRACT



A reaction of 3-chloro-1,2,4-oxadiazoles with allylamine and diallylamine has been investigated. 3,3a,4,5-Tetrahydroisoxazolo[3,4-d]pyrimidines are produced through a tandem ANRORC/[3 + 2]cycloaddition pathway consisting of the addition of allylamine to the 1,2,4-oxadiazole, followed by ring opening, nitron formation, and finally cycloaddition. 3-N-Allylamino-1,2,4-oxadiazoles were also obtained as minor products through a classical SNAr. Conversely, a reaction with diallylamine produces 3-N,N-diallylamino-1,2,4-oxadiazole and imidazoline through tandem SNAr/aziridination and nucleophilic ring opening.

ANRORC (Addition of a Nucleophile, Ring Opening, and Ring Closure) reactions represent a useful strategy for ring transformation of heterocyclic systems.¹ ANRORC rearrangements of six-membered heterocycles have been extensively studied by Van der Plas and co-workers,¹ while ANRORC reactions of five-membered systems concern electron-poor heterocycles such as 1,3,4-oxadiazoles,² 1,3,4-thiadiazoles,³ nitroimidazoles,^{2,4} bis(1,3,4-thiadiazol-2-yl)-1,3,5-triazinium halides,⁵ isothiazole,⁶ and isoxazoles.⁷

Taking advantage of 1,2,4-oxadiazole reactivity and their high tendency to rearrange,⁸ we have reported the

preparation of several fluorinated heterocycles (i.e., 1,2,4-triazoles,⁹ 1,2,4-oxadiazoles,¹⁰ 1,2,4-triazines,^{9b,11} 1,2,4-oxadiazinones,¹² indazoles¹³) via ANRORC reactions.

In this context, the presence of a strongly electron-withdrawing fluorinated group, linked at the C(5) of 1,2,4-oxadiazoles, has been so far considered as “*conditio sine qua non*” for the ANRORC reactivity. Only recently, we have demonstrated the ANRORC reactivity of 3-chloro-1,2,4-oxadiazoles also in the absence of C(5)-linked electron-withdrawing groups.¹⁴ In the latter case, it was suggested that the presence of a chlorine linked at C(3) of the

- (1) Van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, 74, 1–253.
- (2) (a) Hetzheim, A.; Möckel, K. *Adv. Heterocycl. Chem.* **1966**, 7, 183–224. (b) Reid, J. R.; Heindel, N. D. *J. Heterocycl. Chem.* **1976**, 13, 925–926.
- (3) Sandström, J. *Adv. Heterocycl. Chem.* **1968**, 9, 165–209.
- (4) Suwinski, J.; Pawlus, W.; Salwinska, E.; Swierczek, K. *Heterocycles* **1994**, 37, 1511–1520.
- (5) Wermann, K.; Walther, M.; Günther, W.; Görls, H.; Anders, E. *Tetrahedron* **2005**, 61, 673–685.
- (6) Ioannidou, H. A.; Koutentis, P. A. *Tetrahedron* **2009**, 65, 7023–7037.
- (7) (a) Adamo, M. F. A.; Duffy, E. F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron* **2007**, 63, 2047–2052. (b) Adamo, M. F. A.; Duffy, E. F.; Donati, D.; Sarti-Fantoni, P. *Tetrahedron* **2007**, 63, 2684–2688. (c) Adamo, M. F. A.; Donati, D.; Sarti-Fantoni, P.; Buccioni, A. *Tetrahedron Lett.* **2008**, 49, 941–944.
- (8) Pace, A.; Pierro, P. *Org. Biomol. Chem.* **2009**, 7, 4337–4348.

- (9) (a) Buscemi, S.; Pace, A.; Pibiri, I.; Vivona, N.; Spinelli, D. *J. Org. Chem.* **2003**, 68, 605–608. (b) Buscemi, S.; Pace, A.; Palumbo Piccionello, A.; Pibiri, I.; Vivona, N.; Giorgi, G.; Mazzanti, A.; Spinelli, D. *J. Org. Chem.* **2006**, 71, 8106–8113. (c) Palumbo Piccionello, A.; Pace, A.; Buscemi, S.; Vivona, N. *ARKIVOC* **2009**, vi, 235–244.
- (10) Buscemi, S.; Pace, A.; Pibiri, I.; Vivona, N.; Lanza, C. Z.; Spinelli, D. *Eur. J. Org. Chem.* **2004**, 974–980.
- (11) Buscemi, S.; Pace, A.; Palumbo Piccionello, A.; Macaluso, G.; Vivona, N.; Spinelli, D.; Giorgi, G. *J. Org. Chem.* **2005**, 70, 3288–3291.
- (12) Palumbo Piccionello, A.; Pace, A.; Buscemi, S.; Vivona, N.; Giorgi, G. *Tetrahedron Lett.* **2009**, 50, 1472–1474.
- (13) (a) Palumbo Piccionello, A.; Pace, A.; Pibiri, I.; Buscemi, S.; Vivona, N. *Tetrahedron* **2006**, 62, 8792–8797. (b) Palumbo Piccionello, A.; Pace, A.; Pierro, P.; Pibiri, I.; Buscemi, S.; Vivona, N. *Tetrahedron* **2009**, 65, 119–127.
- (14) Palumbo Piccionello, A.; Guarcello, A.; Buscemi, S.; Vivona, N.; Pace, A. *J. Org. Chem.* **2010**, 75, 8724–8727.

oxadiazole ring leads to the formation of a chloro-oxime intermediate after the ring opening induced by the attack of the nucleophile. Considering that such an intermediate could represent a nitrile oxide precursor, we envisaged the possibility of a tandem ANRORC/[3 + 2]cycloaddition reaction with nucleophiles containing an olefinic moiety (Figure 1).

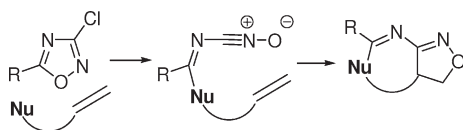


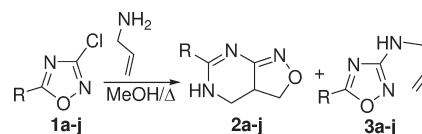
Figure 1. Schematic representation for the tandem ANRORC/[3 + 2]cycloaddition reaction.

Such an approach represents a new entry for the obtainment of heteroannulated isoxazoles¹⁵ by using 3-chloro-1,2,4-oxadiazoles as a masked nitrile oxide. Here we report the study of the reaction of 3-chloro-1,2,4-oxadiazoles **1**, with allylamine as an olefin-tethered nucleophile. Selected 3-chloro derivatives **1a–j**, variously substituted at C(5), were obtained from the corresponding 3-amino-1,2,4-oxadiazoles.^{14,16} Compounds **1** were reacted in refluxing methanol in the presence of a 15-fold excess of allylamine giving tetrahydro-isoxazolo[3,4-*d*]pyrimidines **2**, as major products, together with 3-*N*-allylamino-1,2,4-oxadiazoles **3** (Table 1). All reactions were performed for 9 h, except that for compound **1i** (Table 1, entry 9) which reached 100% conversion in 3 h. Complete conversion of the starting material, after 9 h of heating, was not achieved for those derivatives bearing an electron-donating group linked at C(5) of the oxadiazole ring (Table 1, entries 2, 3, 8, 10), while prolonged reflux (> 9 h) caused formation of degradation products.

From a mechanistic point of view, the formation of the observed products **2** and **3** could be ascribed to the presence of two competing reaction pathways both involving an initial attack of allylamine on the oxadiazole ring (Scheme 1).

In route a (Scheme 1), and in analogy to ANRORC reactions reported for 1,2,4-oxadiazoles,^{9–14} the initial nucleophilic attack on the C(5) of the oxadiazole ring causes ring opening into chloro-oxime intermediate **4**. Subsequent elimination of HCl leads to the *in situ* formation of the nitrile oxide intermediate **5** which, through a [3 + 2] heterocyclization, yields tetrahydro-

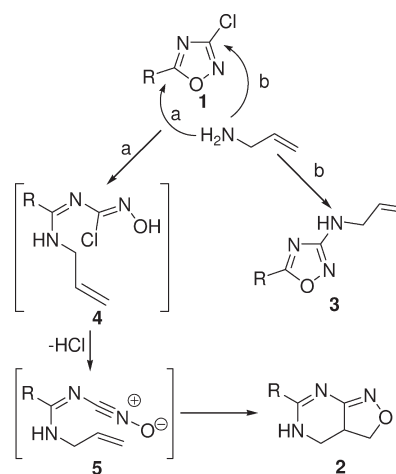
Table 1. Products Distribution for Reaction of Compounds **1** with Allylamine



entry	Reactant	R	2 yield (%) ^a	3 yield (%) ^a
1	1a	Ph	56	35
2	1b (60) ^b	4-MeOPh	21	14
3	1c (58) ^b	4-MePh	16	10
4	1d	4-ClPh	85	14
5	1e	4-NO ₂ Ph	68	18
6	1f	4-CF ₃ Ph	77	19
7	1g	2-furanyl	57	14
8	1h (19) ^b	2-thiophenyl	61	18
9	1i ^c	4-pyridyl	63	33
10	1j (36) ^b	benzyl	40	19

^a Isolated yield. ^b Recovered substrate. ^c Reaction time: 3 h.

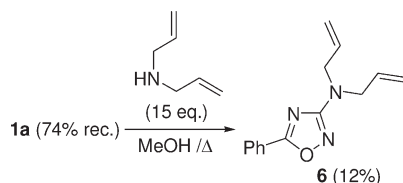
Scheme 1. Proposed Mechanism for the Reactions of **1** with Allylamine



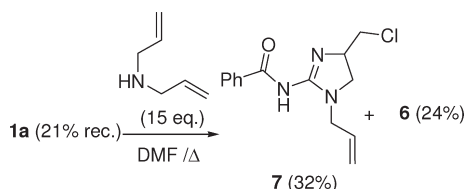
isoxazolo[3,4-*d*]pyrimidines **2**. Conversely, initial attack of the allylamine nitrogen on C(3) (Scheme 1, route b) leads to *N*-allylamino-oxadiazoles **3**, through a classic S_NAr.^{16a} This mechanistic rationale is supported by product distribution data, where compounds bearing electron-withdrawing groups linked at C(5) of the oxadiazole ring gave a higher conversion of starting materials **1** and higher yields of isoxazolo-pyrimidines **2**. In order to consider the effect of the amine structure on the reaction outcome, we have considered the reactivity of representative compound **1a** with *N,N*-diallylamine under the previously reported conditions (9 h, refluxing MeOH) (Scheme 2).

(15) (a) Chiacchio, U.; Corsaro, A.; Rescifina, A.; Bkaithan, M.; Grassi, G.; Piperno, A.; Privitera, T.; Romeo, G. *Tetrahedron* **2001**, *57*, 3425–3433. (b) Alcaide, B.; Almendros, P.; Sàez, E. *Arkivoc* **2004**, iv, 137–152. (c) Sengupta, J.; Mukhopadhyay, R.; Bhattacharjya, A.; Bhadbbhade, M. M.; Bhosekar, G. V. *J. Org. Chem.* **2005**, *70*, 8579–8582. (d) Ghorai, S.; Mukhopadhyay, R.; Kundu, A. P.; Bhattacharjya, A. *Tetrahedron* **2005**, *61*, 2999–3012. (e) Chatterjee, N.; Pandit, P.; Halder, S.; Patra, A.; Mait, D. K. *J. Org. Chem.* **2008**, *73*, 7775–7778.

(16) (a) Eloy, F.; Deryckere, A.; Van Overstraeten, A. *Bull. Soc. Chim. Bel.* **1969**, *78*, 47–53. (b) Fontana, G.; Palumbo Piccionello, A. *Tetrahedron Lett.* **2011**, *52*, 884–886.

Scheme 2. Reaction of Compound **1a** with Diallylamine

In this case only the S_NAr product **6** was obtained in low yield (12%), thus suggesting that with a hindered nucleophile the ANRORC pathway is suppressed. When the reaction was conducted under more forcing conditions, in refluxing DMF, the yield of compound **6** was doubled and the unexpected imidazoline **7** was obtained as a major product (Scheme 3). From a mechanistic point of view, formation of imidazoline **7** could be explained on the basis of the initial formation of amino-substituted oxadiazole **6** followed by a thermally induced breaking of the O–N bond of the 1,2,4-oxadiazole ring, leading to the nitrene

Scheme 3. Thermal Rearrangement of **1a** in the Presence of Diallylamine

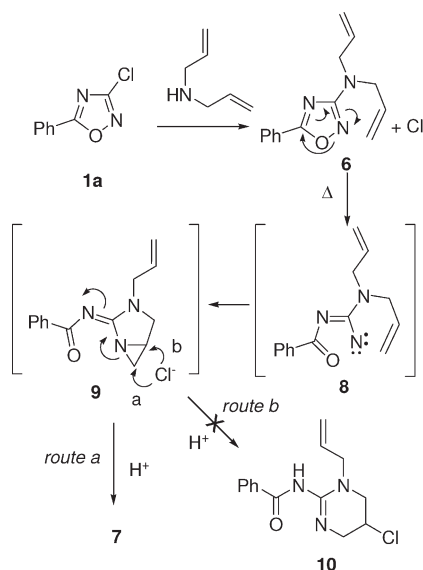
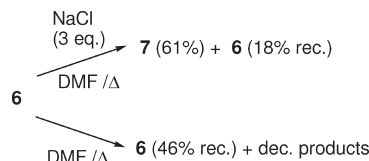
intermediate **8** (Scheme 4). Intramolecular aziridination leads to the formation of a bicyclic intermediate **9** (Scheme 4). Intermediate **9** leads to final imidazoline **7** through regioselective aziridine ring opening by action of chloride on the less hindered carbon (Scheme 4, route a), while pyrimidine derivative **10**, obtainable from the competitive attack of chloride, was not observed (Scheme 4, route b) according to previously reported results for aziridine ring opening by a halide ion.¹⁷ Formation of imidazoline **7** was also observed from thermal rearrangement of oxadiazole **6** in refluxing DMF in the presence of an excess of chloride, while thermal treatment of compound **6** in the absence of a chloride ion did not allow isolation of bicyclic intermediate **9**, probably due to decomposition during workup (Scheme 5).

It is interesting to note that the aziridination of N(2) of the 1,2,4-oxadiazole ring was previously observed just as photochemical intermolecular¹⁸ or intramolecular¹⁹ reactivity. Thus, the reported reactivity represents the first

(17) As a recent example, see: Proust, N.; Gallucci, J. C.; Paquette, L. A. *J. Org. Chem.* **2008**, *73*, 6279–6282.

(18) Palumbo Piccionello, A.; Pibiri, I.; Pace, A.; Raccuglia, R. A.; Buscemi, S.; Vivona, N.; Giorgi, G. *Heterocycles* **2007**, *71*, 1529–1537.

(19) Palumbo Piccionello, A.; Pace, A.; Pibiri, I.; Buscemi, S. *ARKI-VOC* **2009**, *vii*, 156–167.

Scheme 4. Proposed Mechanism for the Formation of Imidazoline **7****Scheme 5.** Thermal Rearrangements of **6**

entry of thermally induced aziridination of the 1,2,4-oxadiazole ring acting as a nitrene equivalent.

In conclusion, the reactivity of 3-chloro-1,2,4-oxadiazoles with allylamines was investigated, showing two novel thermal rearrangements. Reaction with allylamine yielded tetrahydro-isoxazolo[3,4-*d*]pyrimidines **2**, which, to the best of our knowledge, has not been previously reported in the literature. With respect to previously reported ANRORC rearrangements where the ring-closure step consists of an intramolecular cyclocondensation reaction, a novel tandem ring opening/[3 + 2] dipolar cycloaddition is reported. Moreover, reaction with diallylamine allowed the obtainment of highly substituted imidazoline through an unprecedented thermally induced intramolecular aziridination.

Acknowledgment. Financial support through the University of Palermo is gratefully acknowledged.

Supporting Information Available. Synthetic details, characterization data, and ^1H – ^{13}C NMR spectra of compounds **2**, **3**, **6**, and **7**. This material is available free of charge via the Internet at <http://pubs.acs.org>.