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Synthesis of Amino-1,2,4-triazoles by Reductive ANRORC Rearrangements of 1,2,4-Oxadiazoles

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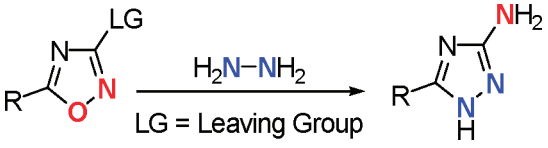
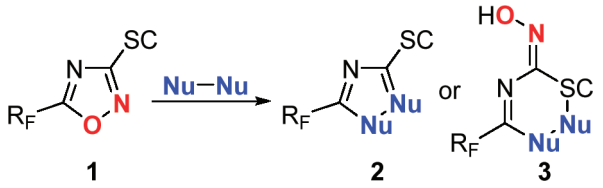


The reaction of various 1,2,4-oxadiazoles with an excess of hydrazine in DMF has been investigated. 3-Amino-1,2,4-triazoles are produced through a reductive ANRORC pathway consisting of the addition of hydrazine to the 1,2,4-oxadiazole followed by ring-opening, ring-closure, and final reduction of the 3-hydroxylamino-1,2,4-triazole intermediate. The general applicability of 1,2,4-oxadiazoles ANRORC reactivity is demonstrated also in the absence of C(5)-linked electron-withdrawing groups.

Heterocyclic rearrangements represent a powerful tool for the synthesis of heterocycles which are difficult to obtain through classical methodologies.[1,2] In this context, ANRORC (Addition of a Nucleophile, Ring-Opening and Ring-Closure) reactions represent a useful strategy for ring transformation of heterocyclic systems.[2] ANRORC rearrangements of six-membered heterocycles have been extensively studied by Van der Plas and co-workers.[2] Whether classified as ANRORC or not, similar ring transformations have been reported for

SCHEME 1. ANRORC of 1,2,4-Oxadiazoles with Dinucleophiles



five-membered heterocycles and are recently gaining importance from both a mechanistc and synthetic point of view.[3−13] These include reactions on electron-poor five-membered systems such as 1,3,4-oxadiazoles,[3] 1,3,4-thiadiazoles,[4] nitroimidazoles,[3,5] bis(1,3,4-thiadiazol-2-yl)-1,3,5-triazinium halides,[6] isothiazole,[7] and isoxazoles.[8] Recently, by taking advantage of 1,2,4-oxadiazoles reactivity and their high tendency to rearrange into more stable heterocycles,[1,14] we have reported several ANRORC rearrangements of fluorinated-1,2,4-oxadiazoles as a valid approach for the obtaining fluorinated heterocycles such as 1,2,4-triazoles,[9] 1,2,4-oxadiazoles,[10] 1,2,4-triazines,[9b,11] 1,2,4-oxadiazinones,[12] and indazoles.[13] In all of these reactions the 1,2,4-oxadiazole substrate acts as a dielectrophile and at least one of its ring atoms, generally the C(5), undergoes nucleophilic attack by the bidentate reagent. The product is a function of the leaving group, which could be internal, i.e. the O(1)−N(2) moiety leading to loss of hydroxylamine,[9,10] or part of the C(3)-[11,12] or C(5)-linked[13] side chain. On the other hand, the effect of a leaving group directly linked to C(3) has not been studied.

In this context, ANRORC reactivity of 1,2,4-oxadiazoles has been so far ascribed to the presence of a strongly electron-withdrawing fluorinated group (R_F) linked at the C(5). Moreover, the identity of the final ring depended on the nature of the side chain (SC) (Scheme 1). However, the possibility to exploit ANRORC of differently substituted (or nonfluorinated) 1,2,4-oxadiazoles was never evaluated.

Here we report the study of the hydrazinolysis reaction of 1,2,4-oxadiazoles **4a**−**m**[15] as a function of solvent, of the nature of the C(3)-linked leaving group (LG), and of the C(5)-linked substituent (Chart 1).

(1) See, for example: (a) Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Heterocycl. Chem.* **1981**, *29*, 141–169. (b) Vivona, N.; Buscemi, S.; Frenna, V.; Cusmano, G. *Adv. Heterocycl. Chem.* **1993**, *56*, 49–154. (c) Pace, A.; Pibiri, I.; Buscemi, S.; Vivona, N. *Heterocycles* **2004**, *63*, 2627–2648. (d) Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds. *Comprehensive Heterocyclic Chemistry III*; Pergamon: Oxford, UK, 2008.

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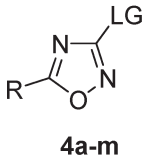
CHART 1



4a-m

a LG = Cl; R = Ph
b LG = OMe; R = Ph
c LG = N(Me)NH_2; R = Ph
d LG = NH_2; R = Ph
e LG = NMe_2; R = Ph
f LG = Cl; R = 4-MePh
g LG = Cl; R = 4-MeOPh
h LG = Cl; R = 4-ClPh
i LG = Cl; R = 4-CF_3Ph
j LG = Cl; R = benzyl
k LG = Cl; R = 2-furanyl
l LG = Cl; R = 2-thiophenyl
m LG = Cl; R = 4-Pyridyl

Selected 3-chloro derivatives **4a** and **4f**−**m**, variously substituted at C(5), were obtained from the corresponding 3-amino-1,2,4-oxadiazoles.[15]

When compound **4a**[15a] was reacted according to previously reported conditions,[9a] i.e., in methanol at room temperature and in the presence of a 5-fold excess of hydrazine, no product formation was observed. Moreover, when reacted in DMF with a stoichiometric amount of hydrazine, compound **4a** remained essentially unchanged.[16] Nevertheless, optimization of reaction conditions, which considered various solvents, temperatures, and reaction times (see the Supporting Information), indicated DMF as an ideal solvent to perform room temperature hydrazinolysis reaction with a 40-fold excess of hydrazine.

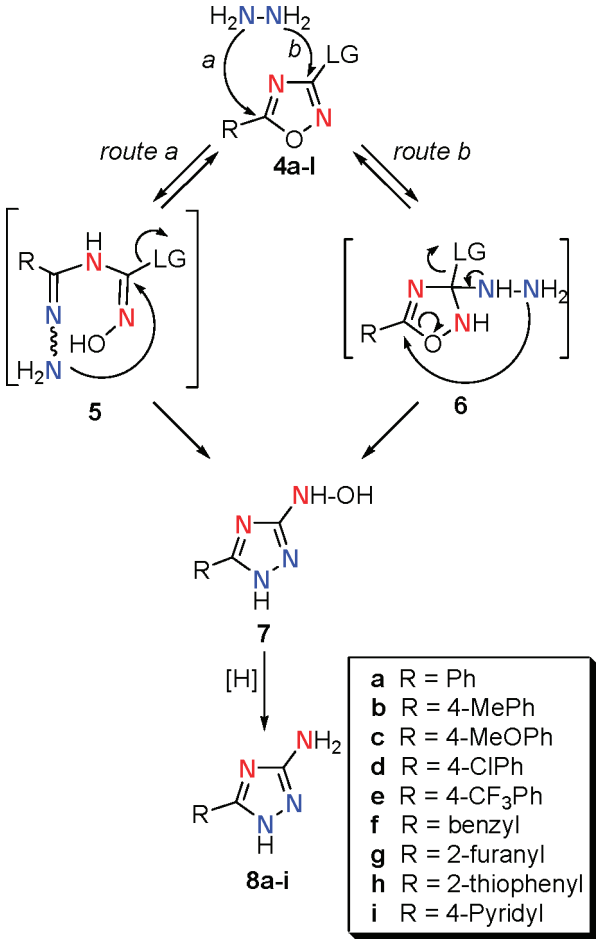
The observed reactivity is illustrated in Scheme 2 for all substrates and results are summarized in Table 1.

The isolation of 3-aminotriazoles **8** is likely a consequence of the reductive reaction environment that transforms the 3-hydroxylamino moiety of intermediate **7** into the 3-amino group of the final product. We were able to isolate a very low amount (5%) of intermediate **7** (R = Ph) under milder conditions from the reaction of the 3-chloro derivative **4a** with hydrazine (5 equiv) in THF. In turn, in a separate reaction with hydrazine, compound **7** (R = Ph) was immediately and quantitatively transformed into the corresponding 3-aminotriazole **8a**.

From a mechanistic point of view and according to reported reactivity of structurally similar isothiazoles[7] and oxadiazoles,[3,9−13] the formation of aminotriazoles **8** could be explained on the basis of two different ANRORC reaction paths involving initial attack of hydrazine on the oxadiazole ring. In route a (Scheme 2), and in analogy to ANRORC reported for 5-perfluoroalkyl-1,2,4-oxadiazoles, the initial nucleophilic attack on the C(5) of the oxadiazole ring causes ring-opening into intermediate **5**. Subsequent ring-closure involving the former C(3) of the oxadiazole with loss of the leaving group leads to hydroxylaminotriazole **7**, which is then reduced into aminotriazole **8**. In route b (Scheme 2), the initial attack involves the C(3) of the oxadiazole leading to the dihydrooxadiazole derivative **6**. This intermediate can produce **7** through nucleophilic attack at C(5), ring-opening

(16) Trace amounts of 3-*N*,*N*-dimethylamino-5-phenyl-1,2,4-oxadiazole, originating from a nucleophilic aromatic substitution of the 3-chloro substituent by the solvent released dimethylamine, were observed.

SCHEME 2. Reaction of Oxadiazoles 4 with Hydrazine



a R = Ph
b R = 4-MePh
c R = 4-MeOPh
d R = 4-ClPh
e R = 4-CF_3Ph
f R = benzyl
g R = 2-furanyl
h R = 2-thiophenyl
i R = 4-Pyridyl

TABLE 1. Reaction of 4 with hydrazine in DMF

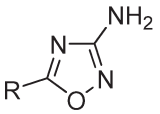
compd	LG	R	time (h)	conv (%)		yield (%)
4a	Cl	Ph	2	100	**8a**	90
4b	OMe	Ph	48	84	**8a**	69
4c	N(Me)NH_2	Ph	48	57	**8a**	51
4d	NH_2	Ph	72	35	**8a**	21
4e	$N(Me)_2$	Ph	72	12	**8a**	8
4f	Cl	4-MePh	2	100	**8b**	85
4g	Cl	4-MeOPh	2	100	**8c**	80
4h	Cl	4-ClPh	2	100	**8d**	75
4i	Cl	4-CF3Ph	2	100	**8e**	71
4j	Cl	benzyl	2	100	**8f**	72
4k	Cl	2-furanyl	2	100	**8g**	93
4l	Cl	2-thiophenyl	2	100	**8h**	86
4m	Cl	4-pyridyl	2	100	**8i**	78

and ring-closure involving either the intramolecular 3-hydrazino moiety or another external hydrazine molecules.

Theoretically, the two proposed routes (Scheme 2) could be concurrent; however, any attempt to isolate 3-hydrazino adduct **6** failed. Surprisingly, the expected formation of 3-hydrazino-1,2,4-oxadiazoles was not evidenced in any of the tested reactions. Such compounds, if formed, should have shown a reactivity similar to that of compound **4c**, which was reported as the exclusive product from the reaction of **4a** with methylhydrazine.[15f]

Compared with 3-chloro-derivative **4a**, instead, 3-methoxy-, 3-amino-, 3-*N*-amino-*N*-methylamino- and 3-dimethylamino-derivatives showed prolonged reaction times, lower

CHART 2



9a-e

a: R = 4-CF_3Ph
b: R = benzyl
c: R = 2-furanyl
d: R = 2-thiophenyl
e: R = 4-Pyridyl

conversion of starting oxadiazole, and lower yield of final triazoles **8**. Therefore, the observed reactivity **4a** > **4b** > **4c** > **4d** > **4e** seems to be strongly dependent on the leaving group ability of the C(3) substituent rather than on its electronic effect. Indeed, neither 3,5-diphenyl-, bearing a conjugating C(3) substituent, nor 3-trifluoromethyl-5-phenyl-1,2,4-oxadiazole, bearing an electron-withdrawing C(3) substituent, reacted under similar conditions.[9a]

On the other hand, there appears to be no correlation between isolated yields of triazoles **8a**−**i** and the type of substitution at the C(5) of the oxadiazole's ring. In fact, all 3-chloro-derivatives **4a** and **4f**−**m** reacted quantitatively within 2 h without any significant difference in the time required to observe complete conversion of the substrate.

In conclusion, the hydrazinolysis of 1,2,4-oxadiazole derivatives **4** containing a leaving group directly linked at the C(3) of the ring was investigated and an easy rearrangement into amino-triazoles **8** through a reductive ANRORC was evidenced. While previous studies have limited the application of ANRORC rearrangements of 1,2,4-oxadiazoles to fluorinated substrates, the reported results introduce the first ANRORC reaction of nonfluorinated 1,2,4-oxadiazoles. Besides opening the way to further mechanistic studies, the high yields obtained suggest considering this methodology as a general approach for the designed synthesis of functionalized aminotriazoles which are well-known for their biological activity.[17]

Experimental Section

Materials and Methods. Melting points were determined on a hot-stage apparatus and are uncorrected. FT-IR spectra were registered in Nujol mull. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 62.5 MHz, respectively, using TMS as an internal standard. Flash chromatography was performed by using silica gel (0.040−0.063 mm) and mixtures of ethyl acetate and petroleum ether (fraction boiling in the range of 40−60 °C) in various ratios. Compounds **4a**,**b**,[15a] **4c**,[15f] **4d**,[15b] **4e**,[15e] and **4f**−**h**[15a] were obtained as previously reported.

General Procedure for the Synthesis of 3-Chloro-1,2,4-oxadiazoles 4i−m. Compounds **4i**−**m** were obtained adapting a previously reported method.[15a]

To a stirred solution of the appropriate amine **9a**−**e**[15b−d] (Chart 2) (10 mmol) in concentrated HCl (50 mL) at 0 °C was added $NaNO_2$ (11 mmol, 0.759 g) portion wise during 1 h. The mixture was kept at rt until gas evolution ceased. Reaction mixture was extracted with $CHCl_3$, the organic phase was dried with $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. Chromatography of the residue allowed isolation of the corresponding 3-chloro-1,2,4-oxadiazoles **4i**−**m** in good yields.

3-Chloro-5-(4-trifluoromethylphenyl)-1,2,4-oxadiazole, 4i: 1.93 g, 68%; mp 66−67 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, 2H, J = 11.4 Hz), 8.24 (d, 2H, J = 11.4 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 123.2 (q, J = 271 Hz), 126.3, 128.1, 128.5, 135.0 (q, J = 32.8 Hz), 162.2, 175.8; IR (Nujol) 1616, 1592 cm^{-1}; GC−MS (m/z) 250 [(M + 2)$^+$, 34%], 248 (M$^+$, 100%). Anal. Calcd for $C_9H_4ClF_3N_2O$: C, 43.48; H, 1.62; N, 11.27. Found: C, 43.50; H, 1.60; N, 11.25.

3-Chloro-5-benzyl-1,2,4-oxadiazole, 4j: 1.14 g, 59%; oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (s, 2H), 7.30−7.35 (m, 5H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 33.3, 128.0, 129.0, 129.1, 132.5, 161.4, 180.2; IR (Nujol) 1568 cm^{-1}; GC−MS (m/z) 196 [(M + 2)$^+$, 32%], 194 (M$^+$, 100%). Anal. Calcd for $C_9H_7ClN_2O$: C, 55.54; H, 3.63; N, 14.39. Found: C, 55.50; H, 3.60; N, 14.40.

3-Chloro-5-(2-furanyl)-1,2,4-oxadiazole, 4k: 1.26 g, 74%; mp 83−84 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.63 (dd, 1H, J_1 = 3.6 Hz, J_2 = 1.5 Hz), 6.35 (d, 1H, J = 3.6 Hz), 7.69 (d, 1H, J = 1.5 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 112.8, 118.0, 139.1, 147.6, 161.7, 168.8; IR (Nujol) 3111, 1624, 1540 cm^{-1}; GC−MS (m/z) 172 [(M + 2)$^+$, 33%], 170 (M$^+$, 100%). Anal. Calcd for $C_6H_3ClN_2O_2$: C, 42.25; H, 1.77; N, 16.43. Found: C, 42.25; H, 1.80; N, 16.40.

3-Chloro-5-(2-thiophenyl)-1,2,4-oxadiazole, 4*l*: 1.60 g, 81%; mp 37−39 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21−7.24 (m, 1H), 7.71 (d, 1H, J = 5.1 Hz), 7.93 (d, 1H, J = 3.6 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 124.5, 128.8, 132.9, 133.4, 161.6, 172.8; IR (Nujol) 3080, 1684, 1647, 1593, 1578 cm^{-1}; GC−MS (m/z) 188 [(M + 2)$^+$, 33%], 186 (M$^+$, 100%). Anal. Calcd for $C_6H_3ClN_2OS$: C, 38.62; H, 1.62; N, 15.01. Found: C, 38.65; H, 1.60; N, 15.00.

3-Chloro-5-(4-pyridyl)-1,2,4-oxadiazole, 4m: 1.05 g, 58%; mp 96−97 °C (petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, 2H, J = 3.0 Hz), 8.90 (d, 1H, J = 3.0 Hz); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 121.0, 130.0, 151.3, 162.4, 175.3; IR (Nujol) 1610, 1578, 1543 cm^{-1}; GC−MS (m/z) 183 [(M + 2)$^+$, 34%], 181 (M$^+$, 100%). Anal. Calcd for $C_7H_4ClN_3O$: C, 46.30; H, 2.22; N, 23.14. Found: C, 46.40; H, 2.20; N, 23.20.

General Procedure for the Reaction of 1,2,4-Oxadiazoles 4a−m with Hydrazine. A 2 mL sample of hydrazine hydrate (41 mmol) was added to a stirred solution of oxadiazole **4** (1 mmol) in dry DMF (2 mL) and the mixture was kept at rt for the time reported in Table 1. The solvent was then evaporated under reduced pressure and the residue treated with water, neutralized with 1 M aqueous HCl, and extracted with EtOAc.The organic layer was dried over $MgSO_4$ then filtered, and the solvent was removed under reduced pressure. Chromatography of the residue allowed isolation of the corresponding 3(5)-amino-5(3)-aryl-1,2,4-triazoles **8** (Table 1). For compounds **8a**−**d**,[18] **8f**,[19] and **8g**−**i**[18] spectroscopic data matched those reported in the cited literature.

3(5)-Amino-5(3)-(4-trifluoromethylphenyl)-1,2,4-triazole, 8e: 162 mg, 71%; mp 222−223 °C (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 6.26 (s, 2H, exch. with D_2O), 7.81 (d, 2H, J = 8.4 Hz), 8.14 (d, 2H J = 8.4 Hz), 12.34 (s, 1H, exch. with D_2O); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 129.5 (q, J = 270 Hz), 130.5, 131.0, 133.6 (q, J = 32 Hz), 141.2, 162.4, 162.9; IR (Nujol) 3420, 3291, 3188, 1679, 1640 cm^{-1}; GC−MS (m/z) 228 (M$^+$, 100%). Anal. Calcd for $C_9H_7F_3N_4$: C, 47.37; H, 3.09; N, 24.55. Found: C, 47.40; H, 3.10; N, 24.50.

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Synthesis of 3(5)-Hydroxylamino-5(3)-phenyl-1,2,4-triazole, 7. A 0.24 mL sample of hydrazine hydrate (5 mmol) was added to a stirred solution of oxadiazole **4a** (1 mol, 0.180 g) in THF (10 mL) and the mixture was kept at rt for 24 h. The solvent was then evaporated under reduced pressure and the residue was treated with water, neutralized with 1 M aqueous HCl, and extracted with EtOAc. The organic layer was dried over $MgSO_4$ then filtered, and the solvent was removed under reduced pressure. Chromatography of the residue produced unreacted **4a** (81 mg, 45%), **8a** (74 mg, 46%), and 3(5)-hydroxylamino-5(3)-phenyl-1,2,4-triazole (**7**) (9 mg, 5%).

3(5)-Hydroxylamino-5(3)-phenyl-1,2,4-triazole, 7: mp 238 °C dec (EtOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.38−765 (m, 3H), 7.92 (m, 2H), 9.09 (s, 1H, exch. with D_2O), 9.35 (s, 1H, exch. with D_2O), 12.98 (s, 1H, exch. with D_2O); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 125.5, 128.3, 128.5, 132.5, 157.4, 158.6; IR (Nujol) 3220, 1577 cm^{-1}; GC−MS (*m*/*z*) 176 (M^+, 8%), 160 (M − 16, 100%). Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.60; H, 4.70; N, 31.90.

Reduction of 3(5)-Hydroxylamino-5(3)-phenyl-1,2,4-triazole (7) with Hydrazine. To a stirred solution of **7** (5 mg, 0.3 mmol) in dry DMF (1 mL) was added hydrazine hydrate (40 equiv, 55 μL) and the mixture was stirred at rt for 1 h. The solvent was then evaporated under reduced pressure and the residue was treated with water, neutralized with 1 M aqueous HCl, and extracted with EtOAc.The organic layer was dried over $MgSO_4$ then filtered, and the solvent was removed under reduced pressure. Chromatography of the residue over preparative TLC plates yielded 3(5)-amino-5(3)-phenyl-1,2,4-triazole (**8a**) (4.5 mg, 100%).

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Supporting Information Available: Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.