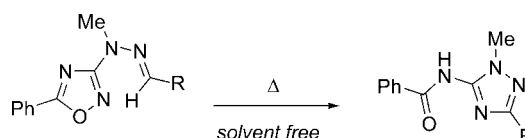


1,2,4-Oxadiazole Rearrangements
Involving an NNC Side-Chain SequenceAntonio Palumbo Piccionello,* Andrea Pace, Silvestre Buscemi, and
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ABSTRACT



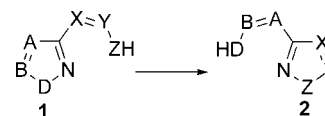
The thermal rearrangement of *N*-1,2,4-oxadiazol-3-yl-hydrazones into 1,2,4-triazole derivatives is reported. This represents the first example of a three-atom side-chain rearrangement involving an NNC sequence linked at the C(3) of the oxadiazole. The reactions carried out under solvent-free conditions produced good to high yields of the final products.

Heterocyclic ring rearrangements are reactions that have been well documented in the literature.¹ Among the most investigated ring-transformation reactions, the Boulton–Katritzky rearrangement (BKR) consists of an interconversion between two five-membered heterocycles where a three-atom side chain and a pivotal annular nitrogen are involved (1→2).²

The reaction has been the subject of numerous synthetic applications^{1c,2,3} and has intriguing mechanistic aspects.⁴

This rearrangement, also classified as an internal nucleophilic substitution,^{3a,b,4a–f,5} typically occurs on 1-oxa-2-azoles (D = O) that are O–N bond-containing heterocycles:

isoxazoles,^{3a,b} 1,2,4-oxadiazoles,³ 1,2,5-oxadiazoles,^{3a,b} and 1,2,5-oxadiazole-2-oxides.^{3b,6}



When the nucleophilic Z atom in the side chain attacks the electrophilic N(2) ring nitrogen, the O(1) ring oxygen

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acts as an internal leaving group, and the O–N bond is cleaved. With Z atoms different from oxygen (for instance, Z = N, S, C), the process is irreversible; the driving force is the formation of a more stable N–N, S–N, or C–N bond replacing the less stable O–N bond.

The only example involving a nucleophilic carbon (Z = C) in an NCC side chain concerned the rearrangement, under basic conditions, of some *N*-(1,2,4-oxadiazol-3-yl)- β -enaminoketones into imidazole.^{7,8} Moreover, although the effect of the type of side chain (X = Y–ZH) on the obtention of different heterocycles has been extensively investigated,^{3b} so far, no study has investigated the involvement of an NNC side chain. Therefore, in the context of our research on heterocyclic rearrangements, we wanted to investigate the occurrence of a BKR in a 1,2,4-oxadiazole series containing a side-chain of the type NNC and possessing a potentially nucleophilic carbon (Z = C).

In this work, we report the rearrangement of *N*-methyl-*N*-(5-phenyl-1,2,4-oxadiazol-3-yl)hydrazones **3** into trisubstituted-1,2,4-triazoles **4** (Figure 1).

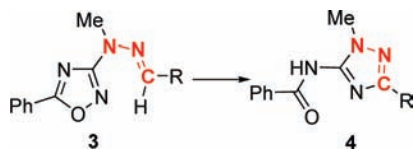
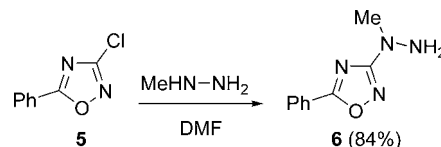


Figure 1. NNC side-chain rearrangement of 1,2,4-oxadiazole.

Selected substrates **3a–i** were obtained in good yield from the condensation of aromatic aldehydes **7a–i** with *N*-methyl-*N*-(5-phenyl-1,2,4-oxadiazol-3-yl)hydrazine **6** (Table 1; for experimental details, see Supporting Informations). In turn, compound **6** was obtained from 3-chloro-5-phenyl-1,2,4-

oxadiazole **5**⁹ through S_NAr with methylhydrazine (Scheme 1). The classic X = Y–ZH sequence in the general BK

Scheme 1. Preparation of Hydrazine **6**



scheme points out the key role of the potentially acidic Z–H proton whose abstraction, under base catalysis conditions, generates the attacking nucleophilic site in the side chain. Our selected substrates lack this structural feature, therefore no catalytic effect should be expected on the reaction of compounds **3** in the presence of a base.

As a matter of fact, an attempt to conduct the rearrangement under basic conditions (*t*-BuOK/DMF) on representative compound **3a** yielded 3-methylamino-5-phenyl-1,2,4-oxadiazole **8**¹⁰ together with benzonitrile and only trace amounts of triazole **4a** (<2%) (Scheme 2).

Scheme 2. Base-Induced Reaction of Compound **3a**

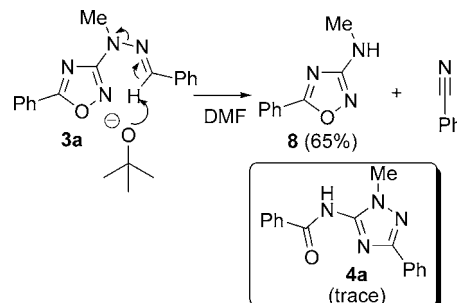
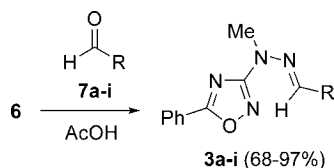


Table 1. Condensation of Hydrazine **6** with Aromatic Aldehydes **7a–i**



entry	product	3 yield% ^a
1	3a R = Ph	83
2	3b R = 4-MePh	97
3	3c R = 4-MeOPh	70
4	3d R = 4-NO ₂ Ph	94
5	3e R = 4-ClPh	93
6	3f R = 4-BrPh	89
7	3g R = 4-CF ₃ Ph	85
8	3h R = 2-thiophenyl	76
9	3i R = 2-furanyl	68

^a Isolated yield.

Formation of oxadiazole **8**, in the presence of *t*-BuOK, could be ascribed to the base-induced cleavage of the hydrazone N–N bond (Scheme 2). On the other hand, heating compounds **3** at reflux in most common organic solvents (toluene, benzene, MeOH, DMF, acetonitrile) generally left the starting material unchanged. Nevertheless, heating compounds **3** for 30 min at temperatures 30 °C higher

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than the corresponding melting point, under solvent-free conditions, yielded 3-(het)arylsubstituted-*N*-1-methyl-5-(*N*-benzoylamino)-1*H*-1,2,4-triazoles **4** (Table 2; for experi-

Table 2. Thermal Rearrangement of Hydrazones **3** into Triazoles **4**

entry	product	4 , yield % ^a	3 (%) ^b
1	4a R = Ph	63	15
2	4b R = 4-MePh	61	18
3	4c R = 4-MeOPh	71	12
4	4d R = 4-NO ₂ Ph	51	28
5	4e R = 4-ClPh	80	10
6	4f R = 4-BrPh	53	21
7	4g R = 4-CF ₃ Ph	99	—
8	4h R = 2-thiophenyl	81	16
9	4i R = 2-furanyl	71	—

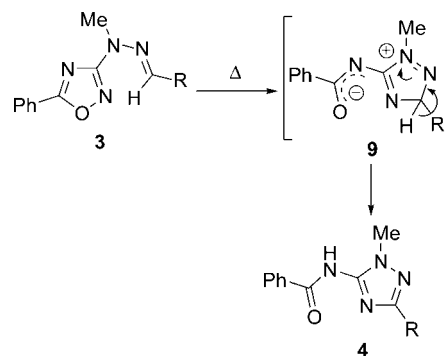
^a Isolated yield. ^b Recovered starting material.

mental details, see Supporting Informations). Despite the fact that total conversion of the starting materials was not achieved for all compounds, prolonged heating was avoided to prevent side-product formation.

From a mechanistic point of view, formation of triazoles **4** can be explained if one invokes the species **9** as a key intermediate (Scheme 3). Such an intermediate could arise either directly from **3**, through a BKR involving the side-chain carbon atom as a nucleophilic site, or from a bicyclic precursor formed from an initial 6 π -assisted heteroelectrocyclic reaction.^{3b} In both cases, the driving force of the reaction could be identified as the higher aromaticity of 1,2,4-triazole ring with respect to 1,2,4-oxadiazole.¹¹

The possibility of other thermal rearrangements already studied for similar substrates (such as a MANC)^{4g} was excluded on the basis of the obtained product.

Scheme 3. Proposed Mechanism for Rearrangement of Compounds **3**



In conclusion, despite a plethora of studies on the Boulton–Katritzky reaction, the reported results introduce the first example of an NNC side chain in this type of rearrangement. Besides opening the way to further mechanistic studies, the precursor accessibility, the solvent-free conditions, the easy workup, and the good product yields allow consideration of this methodology for the designed synthesis of highly functionalized triazolamines which are known for their biological activity.¹²

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

Supporting Information Available: Synthetic details, characterization data, and ¹H–¹³C NMR spectra of compounds **3**, **4**, and **6**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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