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Experimental and DFT Studies on Competitive Heterocyclic Rearrangements. 3.[†] A Cascade Isoxazole−1,2,4-Oxadiazole−Oxazole Rearrangement[‡]

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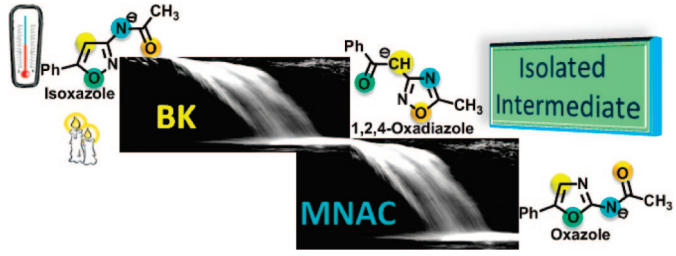
Received September 19, 2008



The thermal rearrangements of 3-acylamino-5-methylisoxazoles **1** have been investigated under basic and neutral conditions and interpreted with the support of computational data. The density functional theory (DFT) study on the competitive routes available for the base-catalyzed thermal rearrangement of isoxazoles **1** showed that the Boulton−Katritzky (BK) rearrangement, producing the less stable 3-acetonyl-1,2,4-oxadiazoles **5**, is a much more favored process than either the migration−nucleophilic attack−cyclization (MNAC) or the ring contraction−ring expansion (RCRE). In turn, an increase in reaction temperature will promote the MNAC of oxadiazoles **5**, producing the more stable 2-acylaminooxazoles **8**. The thermal rearrangement of 3-acylaminoisoxazoles **1** into oxazoles **8** can therefore be interpreted in terms of a cascade BK−MNAC rearrangement involving 3-acetonyl-1,2,4-oxadiazoles **5** as ancillary intermediates.

Introduction

Heterocycles are an important class of organic compounds largely represented in nature and in daily life applications.[1] The knowledge of their properties and chemical behavior is crucial for understanding their functions in biological systems and predicting their features in new materials. Often, heterocyclic compounds are able to undergo chemical transformation into other, more stable, heterocycles. These ring-rearrangements can be either thermally or photochemically induced, and their mechanistic interpretation often represents a challenging research area. Indeed, heterocyclic ring rearrangements are widely documented in the literature[2] and could represent useful synthetic routes to target heterocycles. In the past, when the isolation of intermediates was difficult, mechanisms have been proposed on the basis of the experimental conditions used and of the structure of the final products or by comparison with proven mechanisms for similar reactions.

Nowadays, with the development of continuously more affordable and reliable quantum chemical methods,[3] heterocyclic rearrangements can be described on the basis of theoretical calculations.[4] For example, we recently used combined experimental and computational data to rationalize the mechanisms

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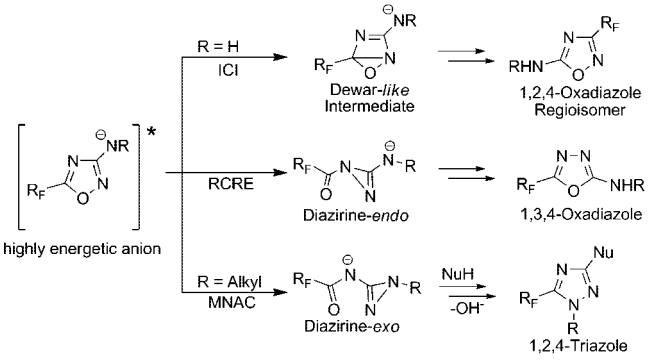
(1) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: Chichester, UK, 1997.

(2) See, for example: (a) Van der Plas, H. C. *Ring Transformation of Heterocycles*, Academic Press: New York, 1973; Vol. 1. (b) Van der Plas, H. C. *Ring Transformation of Heterocycles*; Academic Press: New York, 1973; Vol. 2. (c) L'abbé, G. *J. Heterocycl. Chem.* **1984**, *21*, 627–638. (d) Van der Plas, H. C. *Adv. Heterocycl. Chem.* **1999**, *74*, 1–253. See also specific classes of ring transformations reviewed in: (e) *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vols. 1−8. (f) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier: Amsterdam, 1996; Vols. 1−9.

(3) Cramer, C. J. *Essentials of Computational Chemistry*, 2nd ed.; Wiley: New York, 2004.

10.1021/jo802081k CCC: $40.75 © 2009 American Chemical Society
Published on Web 12/02/2008

SCHEME 1. Reaction Routes Available to the Highly Energetic Anion of 3-Amino(alkylamino)-5-perfluoroalkyl-1,2,4-oxadiazole[7]



of some photochemical[5] and thermal[6] rearrangements involving highly energetic or highly reactive nonisolable intermediates.

In particular, we pointed out that in the photoinduced rearrangements of some 3-amino- and 3-*N*-alkylamino-5-perfluoroalkyl-1,2,4-oxadiazoles, different routes were accessible. In that case, the deprotonation of the neutral excited state of the substrate (about 30 orders of magnitude more acidic than the ground state)[5] could lead to highly energetic excited-state or "hot" ground-state anionic forms. The postphotoexcitation thermochemical development of such intermediates followed a downhill pathway where the internal cyclization−isomerization (ICI), the ring contraction−ring expansion (RCRE), and the migration−nucleophilic attack−cyclization (MNAC) routes were involved in product formation (Scheme 1).[5,7]

Later on, the latter two routes were considered, together with the well-known Boulton−Katritzky (BK) rearrangement,[8] in a combined experimental and theoretical study on the thermal reactivity of the anionic forms of 3-acylamino-1,2,4-oxadiazoles. It was found that the RCRE, the MNAC, and the BK pathways had well-differentiated energetic profiles which allowed thermal control of the observed heterocyclic rearrangement. At temperatures lower than 80 °C, the reversible BK equilibrium was the only active process, while at higher temperatures, the irreversible MNAC rearrangement into the more stable 1,3,4-oxadiazoles was observed. Both these rearrangements involved the N(2) ring-nitrogen as a pivotal electrophilic center,[8] a typical feature of O−N bond-containing azoles.[9] The internal nucleophilic center was represented by either the oxygen atom of the side chain, for the BK rearrangement, or the exocyclic nitrogen atom linked at the C(3) of the oxadiazole ring, for the migration step of the MNAC route. The last two processes of the MNAC rearrangement are then completed in the same step through an intramolecular nucleophilic attack−cyclization involving the oxygen atom of the original side chain (Scheme 2).[6,7]

SCHEME 2. BK, MNAC, and RCRE Routes of the Anionic Forms of 3-Acylamino-1,2,4-oxadiazoles

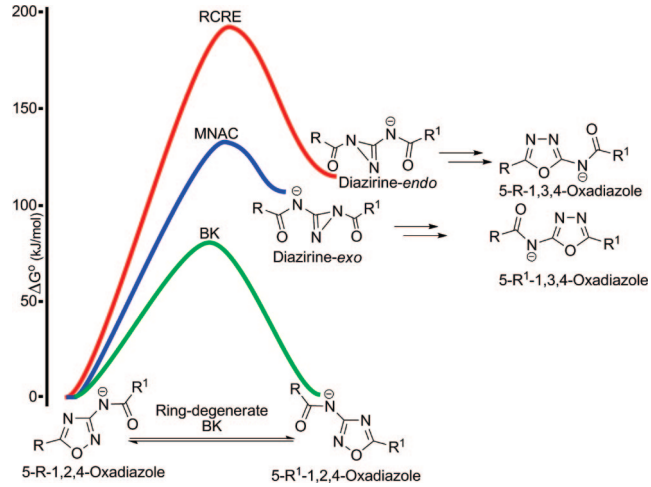
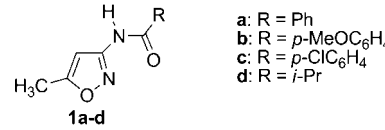


CHART 1



The higher energy demand of the MNAC with respect to the BK can be mainly ascribed to the formation of a ring-strained three-membered cyclic intermediate (diazirine-*exo* in Scheme 2). In this framework, the RCRE route, which also requires the involvement of a three-membered cyclic intermediate (diazirine-*endo* in Scheme 2), is the least favorite one since the cleavage of the O−N(2) ring bond is not assisted by a simultaneous nucleophilic attack on the N(2), such as in the case of BK and MNAC.

Considering the importance of understanding heterocyclic reactivity and of our historical interest in O−N bond-containing azoles, we decided to verify the competition between BK, RCRE, and MNAC rearrangements by studying the thermal reactivity of 3-acylaminoisoxazoles **1a−d** (Chart 1). The substitution of a ring nitrogen atom with a ring C−H group, with respect to previously studied 3-acylamino-1,2,4-oxadiazoles, might in fact cause a significant change of the thermodynamics and kinetics involved along the reaction coordinate.

We proceeded by preliminarily performing an extensive DFT study on the three possible reaction pathways and then by opportunely planning and performing the experiments required to verify the proposed reaction mechanism.

Results and Discussion

3-Acylaminoisoxazoles **1a−d** can, in theory, undergo the same kind of rearrangements observed for 3-acylamino-1,2,4-

(4) For DFT studies on monocyclic BK rearrangements, see: (a) Bottoni, A.; Frenna, V.; Lanza, C. Z.; Macaluso, G.; Spinelli, D. *J. Phys. Chem. A* **2004**, *108*, 1731–1740. Moreover, for DFT studies on bicyclic BK rearrangements, see, for example: (b) Eckert, F.; Rauhut, G. *J. Am. Chem. Soc.* **1998**, *120*, 13478–13484. (c) Rauhut, G. *J. Org. Chem.* **2001**, *66*, 5444–5448. (d) Peña-Gallego, A.; Rodríguez-Otero, J.; Cabaleiro-Lago, E. M. *J. Org. Chem.* **2004**, *69*, 7013–7017.

(5) Pace, A.; Buscemi, S.; Vivona, N.; Silvestri, A.; Barone, G. *J. Org. Chem.* **2006**, *71*, 2740–2749.

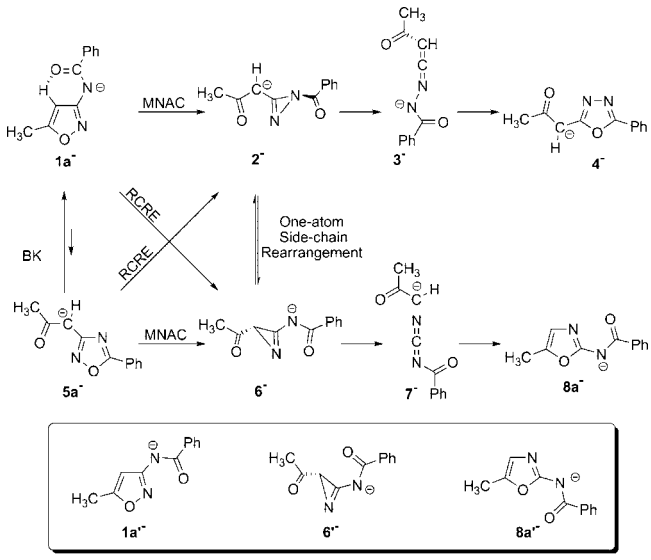
(6) Pace, A.; Pibiri, I.; Palumbo Piccionello, A.; Buscemi, S.; Vivona, N.; Barone, G. *J. Org. Chem.* **2007**, *72*, 7656–7666.

(7) Since in the RCRE route the endocyclic N(4) ring nitrogen is involved in the formation of the diazirine, we named such intermediate as diazirine-*endo*. For the same reason, we named the first MNAC intermediate as diazirine-*exo*, since the exocyclic side-chain nitrogen is involved in its formation.

(8) (a) Boulton, A. J.; Katritzky, A. R.; Hamid, A. M. *J. Chem. Soc. C* **1967**, 2005–2007. (b) Afridi, A. S.; Katritzky, A. R.; Ramsden, C. A. *J. Chem. Soc., Perkin Trans. 1* **1976**, 315–320.

(9) (a) Pace, A.; Pibiri, I.; Buscemi, S.; Vivona, N. *Heterocycles* **2004**, *63* (11), 2627–2648. (b) Ruccia, M.; Vivona, N.; Spinelli, D. *Adv. Heterocycl. Chem.* **1981**, *29*, 141–169. (c) Vivona, N.; Buscemi, S.; Frenna, V.; Cusmano, G. *Adv. Heterocycl. Chem.* **1993**, *56*, 49–154. (d) Korbonits, D.; Kanzel-Szvoboda, I.; Horváth, K. *J. Chem. Soc., Perkin Trans. 1* **1982**, 759–766. (e) Horváth, K.; Korbonits, D.; Naráy-Szabò, G.; Simon, K. *THEOCHEM* **1986**, *136*, 215–227. (f) Boulton, A. J.; Frank, F.; Huckstep, M. R. *Gazz. Chim. Ital.* **1982**, *112*, 181–183. (g) Sheremetev, A. B.; Makhova, N. N.; Friedrichsen, W. *Adv. Heterocycl. Chem.* **2001**, *78*, 66–188. (h) Makhova, N. N.; Ovchinnikov, I. V.; Kulikov, A. S.; Molotov, S. I.; Baryshnikova, E. L. *Pure Appl. Chem.* **2004**, *76*, 1691–1703.

SCHEME 3. BK, MNAC, and RCRE Routes Available to Representative 3-Benzoylamino-5-methylisoxazole 1a in Its Deprotonated Anionic Form 1a⁻



oxadiazoles since they contain an electrophilic N(2) ring nitrogen and two potentially nucleophilic centers in the side chain: the exocyclic nitrogen and the carbonylic oxygen.

A previous report from our laboratories showed that some 3-aroylaminoisoxazoles, heated under basic conditions, rearranged into the corresponding 2-aroylamino-oxazoles with no evidence of the occurrence of other rearrangements.[10] Such reactivity, involving the anionic forms, was interpreted in terms of a RCRE pathway, in analogy to the well-proven mechanism proposed for the photochemical isoxazole−azirine−oxazole transformation.[11] However, based on our recent study showing that the RCRE of 3-acylamino-1,2,4-oxadiazoles is the highest energy demanding among the three possible routes,[6] we were prompted to reinvestigate the base-catalyzed rearrangement of 3-acylaminoisoxazoles **1**. Therefore, we performed a DFT study on the anionic forms of substrates, products, intermediates, and transition states of all of the possible BK, MNAC, and RCRE routes available to the representative compound **1a** (Scheme 3). Moreover, to complete the mechanistic picture, the possibility of a one-atom side-chain rearrangement between the three-membered ring intermediates **2**⁻ and **6**⁻ has been also considered.

Structures and free energy values have been calculated in vacuo in DMSO and MeOH to simulate the presence of polar aprotic or protic solvents.[12] Standard free energy values ($\Delta G°$), relative to **1a**⁻, of reagents, products and transition states, and activation barriers ($\Delta G^{\ddagger}$) are reported in Table 1. Representative data calculated in MeOH are also graphically illustrated in Figure 1.

All possible conformers and tautomers have been considered for each reagent, intermediate, or product; however, only the most stable or particularly significant key structures will be discussed in detail. For instance, the structure **1a**⁻ represents the most stable conformer of the anionic isoxazole reagent, due to the stabilizing hydrogen bond between the amide moiety and the C(4)−H of the heterocycle. Nevertheless, the BK route requires an initial rotation of the C(3)−N bond with formation of the less stable conformer **1a′**⁻ which is an intermediate toward the formation of 1,2,4-oxadiazole **5a**⁻. Similarly, calculations showed how the RCRE route of **1a**⁻ would lead to the formation of the less stable azirine conformer **6′**⁻, accessible also from azirine **6**⁻, precursor of carbodiimide **7**⁻. Furthermore, the development of **7**⁻produces the oxazole **8a′**⁻ which will eventually give **8a**⁻, a more stable conformer in methanol.

Computational results show undoubtedly that the previously claimed RCRE route,[10] due to its high activation barrier ($\Delta G^{\ddagger}$ > 180 kJ/mol in all three media), is not a plausible mechanism for the thermal transformation of isoxazole **1a** into oxazole **8a**; therefore, this rearrangement should be interpreted in terms of a different mechanistic pathway. Another alternative route toward oxazole **8a** (see Scheme 3) consists of a MNAC of isoxazole **1a**⁻ followed by a one-atom side-chain rearrangement of diazirine **2**⁻ leading to **6**⁻ and eventually to **8a**⁻. However, if diazirine **2**⁻ was formed, its development into **3**⁻ and then **4**⁻, with an activation barrier of only $\Delta G^{\ddagger}$ = 38.3∼48.3 kJ/mol, would have been favored over the transformation into azirine **6**⁻ with a $\Delta G^{\ddagger}$ = 64.9∼75.7 kJ/mol.

Moreover, an accurate analysis of data reported in Table 1 reveals a significant change of the activation barrier for the MNAC rearrangement of deprotonated isoxazole **1a**⁻ with respect to previously studied 3-acylamino-1,2,4-oxadiazoles.[6,13] For the general system illustrated in Chart 2, a change in the ring-atom A from N to CH (with B = N) causes a stabilization of the substrate with a consequent increase of the activation barrier of MNAC from 111.7[6] to 142.8 (in vacuo) and from 132.5[6] to 152.7 (in DMSO). This renders the MNAC route less accessible to 3-acylaminoisoxazole **1a** than it is for 3-acylamino-1,2,4-oxadiazoles.

On the other hand, a change in the side-chain atom B from N to CH (with A = N) increases the reactivity of the nucleophilic site and lowers the activation barrier, with respect to 3-acylamino-1,2,4-oxadiazoles, from 103.6[6] to 72.3 (in vacuo) and from 132.1[6] to 95.1 (in DMSO). Therefore, the MNAC route of oxadiazole **5a**⁻ is much more favored than either its RCRE rearrangement or the MNAC of the isoxazole **1a**⁻.

Overall, theoretical data suggest the intriguing hypothesis that the formation of oxazole **8a** originates from a cascade BK−MNAC rearrangement of the substrate **1a**. In other words, deprotonated isoxazole **1a**⁻ will initially rearrange (via BK) into 1,2,4-oxadiazole **5a**⁻ which, in turn, rearranges (via MNAC) into azirine **6**⁻ which will eventually produce the final oxazole **8a**⁻.

To obtain experimental support, the thermal rearrangements of **1a** was performed by heating the substrate in DMF and in the presence of an equimolar amount of *t*-BuOK, and the reaction mixtures were monitored by TLC using authentic synthetic samples of **4**,[14] **5a** (see the Experimental Section), and **8a**[10] as reference compounds. After 1 h at 110 °C, substrate **1a** was partly converted into oxazole **8a**, and a repeatedly eluted TLC[15] revealed the presence of 1,2,4-oxadiazole **5a**, never observed in previous studies.[10,16] Obviously, a similar product

(10) Buscemi, S.; Frenna, V.; Vivona, N. *Heterocycles* **1991**, *32*, 1765–1772.

(11) (a) Ullman, E. F.; Singh, B. *J. Org. Chem.* **1966**, *31*, 1844–1845. (b) Ullman, E. F.; Singh, B. *J. Org. Chem.* **1967**, *32*, 6911–6916. (c) Singh, B.; Zweig, A.; Gallivan, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 1199–1206.

(12) This choice also allows an easier comparison with previously calculated data for similar reactions such as photoinduced MNAC and RCRE in MeOH (see ref 5) and thermal BK, MNAC, and RCRE in DMSO (see ref 6).

(13) A complete comparison table between activation barriers of BK, MNAC, and RCRE rearrangements of deprotonated isoxazole **1a**⁻, oxadiazole **5a**⁻, and previously studied 3-acylamino-1,2,4-oxadiazoles is given in the Supporting Information.

(14) Kato, T.; Chiba, T.; Daneshtalab, M. *Chem. Pharm. Bull.* **1976**, *24*, 2549–2552.

TABLE 1. Standard Free Energy Values ($\Delta G°$, kJ/mol) Relative to Compound $1a^-$,[a] for Anionic Species or Transition States, and Activation Barriers ($\Delta G^‡$, kJ/mol), Relative to the Given Starting Compound, Along the Reaction Coordinate, Calculated in Vacuo, in DMSO and in MeOH at 298.15 K

deprotonated species	$\Delta G°$ (in vacuo)	$\Delta G°$ (DMSO)	$\Delta G°$ (MeOH)	transition states	$\Delta G°$ (in vacuo)	$\Delta G°$ (DMSO)	$\Delta G°$ (MeOH)
1a$^-$	0.0	0.0	0.0	[**1a**$^-$→**1a′**$^-$]‡	28.2	18.7	11.6
1a′$^-$	20.9	10.0	3.2	[**1a**$^-$→**2**$^-$]^{‡b}	142.8	152.7	140.4
2$^-$	116.7	127.2	115.2	[**1a**$^-$→**6′**$^-$]^{‡c}	181.6	202.9	190.6
3$^-$	22.2	48.4	39.6	[**1a′**$^-$→**5a**$^-$]‡	96.4	100.0	89.3
4$^-$	−21.8	−20.1	−27.5	[**2**$^-$→**3**$^-$]‡	155.5	173.2	163.5
5a$^-$	31.0	15.6	7.1	[**2**$^-$→**6**$^-$]^{‡c}	181.6	202.9	190.6
6$^-$	1.2	3.0	−14.5	[**3**$^-$→**4**$^-$]‡	48.8	59.6	53.4
6′$^-$	−9.7	3.7	−10.1	[**5a**$^-$→**2**$^-$]^{‡b}	142.8	152.7	140.4
7$^-$	−48.3	−23.3	−33.0	[**5a**$^-$→**6**$^-$]‡	103.3	110.7	99.5
8a′$^-$	−94.5	−90.6	−99.5	[**6**$^-$→**6′**$^-$]‡	14.2	24.7	12.9
8a$^-$	−91.1	−89.8	−104.4	[**6′**$^-$→**7**$^-$]‡	51.4	62.8	50.9
				[**7**$^-$→**8a′**$^-$]‡	−20.4	−7.6	−16.5
				[**8a′**$^-$→**8a**$^-$]‡	−80.7	−78.8	−90.0

reactions	$\Delta G^‡$ (in vacuo)	$\Delta G^‡$ (DMSO)	$\Delta G^‡$ (MeOH)
1a$^-$→**1a′**$^-$	28.2	18.7	11.6
1a$^-$→**2**$^-$	142.8	152.7	140.4
1a$^-$→**6′**$^-$	181.6	202.9	190.6
1a′$^-$→**5a**$^-$	75.5	90.0	86.1
2$^-$→**3**$^-$	38.3	46.0	48.3
2$^-$→**6**$^-$	64.9	75.7	75.4
3$^-$→**4**$^-$	26.6	11.2	13.8
5a$^-$→**2**$^-$	111.8	137.1	133.3
5a$^-$→**6**$^-$	72.3	95.1	92.4
6$^-$→**6′**$^-$	13.0	21.7	27.4
6′$^-$→**7**$^-$	61.1	59.1	61.0
7$^-$→**8a′**$^-$	27.9	15.7	16.5
8a′$^-$→**8a**$^-$	10.4	11.0	14.4

[a] The standard free energy value calculated at B3LYP/6-31++G(d,p) level is −684.47037 au for **1a**$^-$; the solvation free energy values for **1a**$^-$are −50.62 kcal/mol (in DMSO) and −59.85 kcal/mol (in MeOH) (see Computational Details in the Experimental Section). [b] The transformation of either **1a**$^-$ or **5a**$^-$ into **2**$^-$ occurs through the same transition state. [c] The transformations of **1a**$^-$ into **6′**$^-$ and of **2**$^-$ into **6**$^-$ occur through the same transition state.

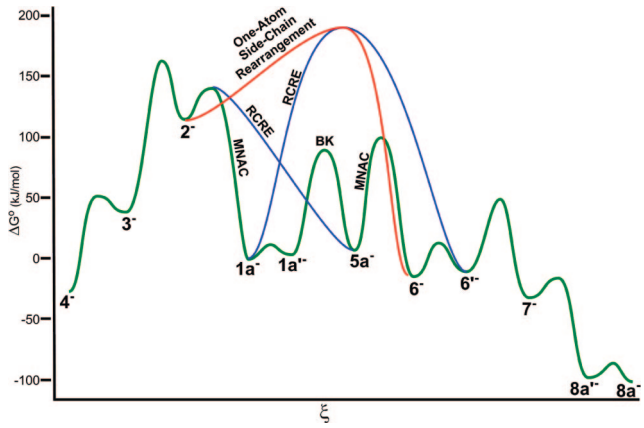
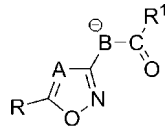


FIGURE 1. Standard free energy profiles along the reaction coordinate of anionic routes of isoxazole **1a** in MeOH solution, at 298.15 K.

CHART 2



distribution was observed during the reaction of oxadiazole **5a** since, under these reaction conditions, it should readily rearrange into isoxazole **1a**. Although the Boulton−Katritzky rearrangement between **1a** and **5a** is potentially a reversible reaction, this result represents the first example of the isolation of the less stable 1,2,4-oxadiazole from a BK rearrangement of isoxazoles.[17] No trace of 1,3,4-oxadiazole **4** was present in either reaction mixture, even after prolonged heating (4 h in refluxing DMF/*t*-BuOK) of the substrate, thus excluding both the MNAC of isoxazole **1a** and the RCRE of oxadiazole **5a** as possible routes.

Also compounds **1b**−**d** yielded the corresponding oxazoles **8b**−**d** in good yield,[16] while traces of 1,2,4-oxadiazoles **5b** and **5c** were detected. On the other hand, during the rearrangement of **1d** into **8d**, no traces of **5d**, which is known to undergo a complete BK transformation into isoxazole **1d**,[18] were detected (Scheme 4).

Interestingly, when the reaction of **1a** was performed at lower temperature in refluxing methanol containing only 0.1 equiv of *t*-BuOK, the formation of oxadiazole **5a** was spotted after 30 min, while oxazole **8a** became detectable after 1 h. This qualitative kinetic observation seemed to support the hypothesis that the formation of oxazole **8a** may occur through the oxadiazole **5a** intermediate. Unfortunately, a quantitative NMR

(15) Any attempt to perform either quantitative or analytical HPLC separation of isoxazole **1a** and oxadiazole **5a** from the reaction mixture was unsuccessful. Moreover, dynamic NMR measurements were precluded by the low solubility of **1a**$^-$ and **5a**$^-$ in DMF-d_6 at the temperature reachable with the instrument. Analytical and preparative TLC were repeatedly eluted in a light petroleum ether/ethyl acetate 5/1 (vol/vol) mixture to achieve satisfactory separation of the two compounds.

(16) The previously reported yields of oxazoles **8a** and **8b** (see also ref 10) were reproduced, within experimental error, after compounds **1a** and **1b** were heated for 4 h at 110 °C in DMF/*t*-BuOK.

(17) In the benzo-condensed series, the formation of 1,2,4-oxadiazoles was reported from a base-catalyzed BK rearrangement of 3-acylaminobenzisoxazoles. Harsányi, K. *J. Heterocycl. Chem.* **1973**, *10*, 957–961.

(18) Kübel, B. *Monatsh. Chem.* **1983**, *114*, 373–376.

SCHEME 4

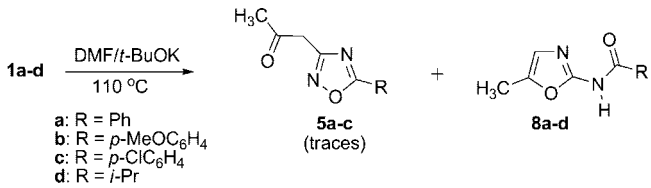


TABLE 2. Mixture Composition (%), Determined by NMR,[a] as a Function of Time (h) for the Reaction of Isoxazole 1a and Oxadiazole 5a in Refluxing Ethanol/*t*-BuOK

reaction time (h)	reaction of isoxazole **1a**			reaction of oxadiazole **5a**		
	1a	**5a**	**8a**	**1a**	**5a**	**8a**
0.5	97.2 ± 0.3	2.8 ± 0.3	≪0.1[a,b]	93.2 ± 0.5	5.0 ± 0.3	1.8 ± 0.2
1.0	95.3 ± 0.5	3.9 ± 0.3	0.8 ± 0.2	93.5 ± 0.5	4.0 ± 0.2	2.5 ± 0.3
2.5	92.1 ± 0.4	3.0 ± 0.3	4.9 ± 0.2	90.0 ± 0.4	4.0 ± 0.3	6.0 ± 0.2
4.0	88.3 ± 0.4	3.0 ± 0.4	8.7 ± 0.3	86.0 ± 0.2	4.0 ± 0.3	10.0 ± 0.4

[a] Under the conditions used (50 mg of substrate), NMR determinations were able to reproduce the composition of a known prepared mixture of **1a** (94%), **5a** (4%), and **8a** (2%) within a 0.2% experimental error and a threshold level of 0.1%. [b] Traces of compound **8a** were detected only by TLC performed on a concentrated sample.

analysis of the reaction mixture was not achievable due to the very low conversion of the substrate at the early stages of the reaction.[15] However, by performing the reaction in refluxing ethanol/*t*-BuOK, substrate conversion was increased[19] enough to allow NMR determination of reaction mixture composition as a function of time (see Table 2).

Data from Table 2 represent the strongest evidence that anionic oxadiazole **5a**$^-$ is a reaction intermediate for the formation of oxazole **8a** from a thermal rearrangement of isoxazole **1a**. In fact, yields in oxazole **8a** are consistently higher from the reaction of **5a** (an advanced starting point along the isoxazole-to-oxazole reaction coordinate) than they are in the reaction of **1a**. In other words, when starting from 100% of **1a**, only the BK rearrangement occurs ($\Delta G^{\ddagger}$ = 86.1 kJ/mol), forming a few percent of the less stable oxadiazole **5a** ($\Delta G°$ = 7.1 kJ/mol); the latter undergoes the "*retro*"-BK rearrangement ($\Delta G^{\ddagger}$ = 82.2 kJ/mol) faster than the MNAC ($\Delta G^{\ddagger}$ = 92.4 kJ/mol); therefore, oxazole **8a** becomes significantly detectable only after 1 h of total reaction time. When starting from 100% of oxadiazole **5a**, instead, the MNAC route was able to produce almost 2% of oxazole **8a** after just 30 min, while the faster BK route yielded 93% of **1a**. Since the BK equilibrium is the fastest among the competitive pathways, the use of either isoxazole **1a** or oxadiazole **5a** as starting compounds makes a significant difference only during the earlier stages of the rearrangements. In fact, after 1 h, both reactions contained about 4% of oxadiazole **5a** and both increased the yield of oxazole **8a** of 7.5% in the next 3 h.

As far as neutral forms are concerned, DFT calculations have been performed on reagent, products, and intermediates along the reaction coordinate of the isoxazole-to-oxazole rearrangement of compound **1a** (see Table 3). Moreover, since an exhaustive computational kinetic study on the competitive mechanisms should consider all coordinates connecting all accessible tautomers and conformers (even the less stable ones)

(19) The higher temperature reached in refluxing ethanol allowed an easier overtake of the activation barriers of both BK (of **1a**$^-$ and **5a**$^-$) and MNAC (of **5a**$^-$) rearrangements, with respect to the reaction carried out in methanol. Moreover, in a previous report (see ref 10), no reaction was observed when **1a** was refluxed in ethanol/KOH medium.

TABLE 3. Standard Free Energy Values ($\Delta G°$, kJ/mol) Relative to Compound 1a,[a] for Neutral Species or Transition States, and Activation Barriers ($\Delta G^{\ddagger}$, kJ/mol), Relative to the Given Starting Compound, Along the Reaction Coordinate, Calculated in Vacuo, in DMSO and in MeOH at 298.15 K

compd	$\Delta G°$ (in vacuo)	$\Delta G°$ (DMSO)	$\Delta G°$ (MeOH)
1a	0.0	0.0	0.0
1a′	27.6	10.0	7.2
2	178.9	179.7	177.0
4	−15.8	−21.4	−23.5
5a^{zw}	158.2	110.1	95.3
5a^{enol}	10.9	19.4	28.7
5a^{keto}	8.0	7.6	6.5
6	60.1	44.6	29.0
7^{zw}	49.5	48.5	40.4
8a	−71.2	−79.2	−82.5
8a^{imino}	−88.7	−87.5	−82.3
transition state	$\Delta G°$ (in vacuo)	$\Delta G°$ (DMSO)	$\Delta G°$ (MeOH)
[**1a′→5a^{zw}**]‡	176.8	136.0	121.7
reactions	$\Delta G^{\ddagger}$ (in vacuo)	$\Delta G^{\ddagger}$ (DMSO)	$\Delta G^{\ddagger}$ (MeOH)
1a′→5a^{zw}	149.2	126.0	114.5

[a] The standard free energy value calculated at B3LYP/6-31++G(d,p) level is −685.00864 au for **1a**; the solvation free energy values for **1a** are −6.01 kcal/mol (in DMSO) and −15.15 kcal/mol (in MeOH) (see Computational Details in the Experimental Section).

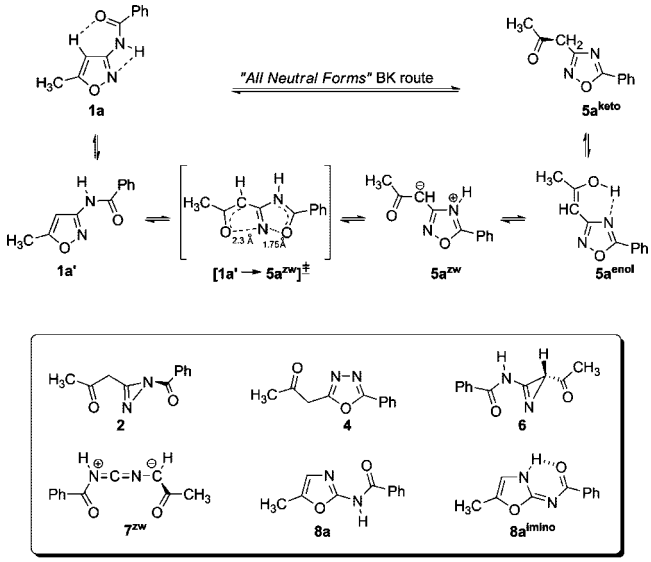
which can be possibly involved, kinetic studies for the search of neutral transition states have been reported only for the BK step. In this frame, we did not consider explicit solvent molecules which could be also involved along the reaction path. As a matter of fact, although 1,3,4-oxadiazole **4** is more stable than either isoxazole **1a** or oxadiazole **5a**, it is by far less stable than oxazole **8a**. Moreover, its diazirine precursor **2** has a free energy (relative to **1a**) of $\Delta G°$ =179.7 kJ/mol. Therefore, in analogy with the anion route, the formation of **4** should be both thermodynamically and kinetically unfavored with respect to the formation of oxazole **8a**.

Similar to the anionic BK route, and starting from the more stable isoxazole **1a**, an initial rotation of the C(3)−$N_{exocyclic}$ bond, yielding **1a′**, is required to achieve the correct geometry to undergo the neutral BK rearrangement. At this point, if one hypothesizes that no proton exchange is involved in the reaction, the BK step will produce the zwitterionic product **5a^{zw}** which could intramolecularly stabilize into its enol form **5a^{enol}** and eventually produce the more stable **5a^{keto}** (Scheme 5).

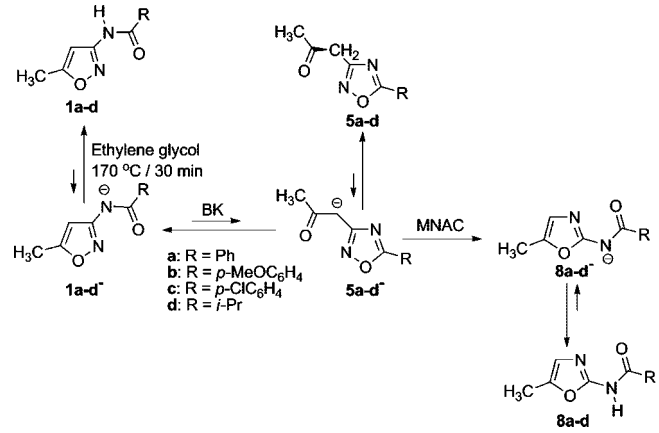
A comparison between data in Tables 1 and 3 shows that the activation barrier of the BK rearrangement is higher for the neutral than for the anionic route, suggesting that higher temperatures are needed just to observe the BK process under neutral conditions. Moreover, while the activation barrier for the anionic BK route increased by increasing the polarity of the reaction media, according to the Hughes and Ingold rules,[20] for the neutral route a stronger and opposite effect is observed suggesting the use of polar solvents. As a matter of fact, no reaction of **1a** was observed in refluxing methanol (bp 65 °C),

(20) The intramolecular reaction between the isoxazole nucleus (neutral substrate) and the side-chain oxygen (anionic nucleophile) occurs through a transition state with charge dispersion. Therefore, the solvent stabilization effect is more pronounced for the reagent than for the transition state and the activation barrier increases with solvent polarity. See: (a) Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1935**, 244–255. (b) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University Press: Ithaca and London, 1969; pp 457−463. (c) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 3rd ed.; Wiley-VCH: Weinheim, 2003; pp 163−173.

SCHEME 5



SCHEME 6



ethanol (bp 78 °C), or *n*-butanol (bp 118 °C), while only traces of 1,2,4-oxadiazoles **5a** and **8a** were detected from the reaction of **1a** by prolonged (8 h) refluxing in DMF (bp 153 °C).[21] Reaction of **1a** performed in a sealed tube and in the absence of solvent at 170 °C for 4 h yielded 5% of 1,2,4-oxadiazole **5a** and 90% of recovered starting material, while oxazole **8a** was only detected in traces.[21] Even lower amounts of **5a** were obtained from the reaction at 170 °C in Ph_2O. On the other hand, when a high boiling protic solvent such as ethylene glycol was used, reaction of **1a** yielded 8% of **5a** and 10% of **8a** together with recovered starting material (61%) and a few amount of ethylene glycol monobenzoate (6%) after just 30 min at 170 °C.

These observations suggest that, besides temperature, the protic medium plays a key role in promoting the reaction, most likely favoring proton exchanges. The formation of oxadiazole **5a** under neutral conditions could be interpreted in terms of a BK rearrangement of the isoxazole **1a** into **5a**^{zw} followed by a solvent mediated, rather than intramolecular, prototropic shift from the amide to the acetonyl moiety (Scheme 5). An alternative hypothesis still considers the anionic form of the starting substrate as the key intermediate which can be formed at high temperatures more easily in protic than in aprotic solvents. In other words, the BK and the MNAC rearrangements observed under neutral conditions could be the results of preliminary acid−base equilibria, where the solvent acts as a proton acceptor, followed by rearrangements of the deprotonated species and final neutralization (Scheme 6).

This hypothesis is also supported by the fact that yields in oxadiazole **5a**−**c** (% yields of **5c** > **5a** > **5b**; see the Experimental Section) increase with the presumed acidity of their isoxazole precursors **1a**−**c**. In fact, while isoxazoles **1a**−**c** remain the major component of the BK equilibrium due to the higher aromaticity of the heterocyclic ring,[22] their acid−base equilibria will tend to be shifted toward the less acidic species 3-acetonyl-1,2,4-oxadiazoles **5a**−**c**. In the case of the isobutyrroylamino derivative **1d**, the formation of 3-acetonyl-5-isopropyl-1,2,4-oxadiazole **5d** was not observed, most likely due to its extremely low concentration. In fact, the free energy difference between **1d** and **5d** is almost double ($\Delta G°_{5d\text{-}1d}$= 13.5 kJ/mol in MeOH)[23] with respect to that of the corresponding phenyl derivatives **5a** and **1a** ($\Delta G°_{5a\text{-}1a}$= 6.5 kJ/mol in MeOH) due to the lack of the stabilizing *diaryloid effect*[24] exerted by the phenyl group on the oxadiazole.

Conclusions

The DFT study on the competitive routes available for the base catalyzed thermal rearrangement of 3-acylaminoisoxazoles **1** showed that the BK reaction is a much more favored process than either the MNAC or the RCRE. This rearrangement produces an equilibrium mixture of 3-acylaminoisoxazole **1** and the corresponding 3-acetonyl-1,2,4-oxadiazole **5**, where the latter is, by far, the minor component. Unlike the previously studied 3-acylamino-1,2,4-oxadiazoles, where the MNACs of both BK equilibrium components had similar activation barriers, here an increase in reaction temperature promotes only the MNAC of oxadiazole **5**, irreversibly producing the more stable oxazole **8**. Therefore, while the photoinduced rearrangement of isoxazoles into oxazoles is well-proven to follow a RCRE route, the thermal rearrangement of 3-acylaminoisoxazoles **1** into 2-acylaminooxazoles **8** should be better interpreted in terms of a cascade BK-MNAC rearrangement involving 3-acetonyl-1,2,4-oxadiazoles **5** as ancillary intermediates. This mechanistic hypothesis is supported by the isolation of oxadiazoles **5** from the reaction mixture as well as by the higher yields in oxazole **8** obtained when oxadiazole **5** is used as starting material. Although the Boulton−Katritzky rearrangement between **1** and **5** could be considered as a potentially reversible equilibrium reaction, this study represents an interesting example of the isolation of the less stable 1,2,4-oxadiazole heterocycle in a BK rearrangement of isoxazoles.

Experimental Section

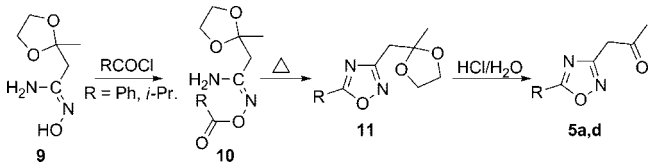
Starting Materials. All chromatographic purification/separations have been performed using silica gel (0.040−0.063 mesh) and mixtures of light petroleum/EtOAc in various ratios. Compounds

(21) In a previous report (ref 10), no reaction was observed by either refluxing **1a** in DMF for 4 h or keeping it in the melted phase at 170 °C for 30 min.

(22) (a) Bird, C. V. *Tetrahedron* **1985**, *41*, 1409–1414. (b) Bird, C. V. *Tetrahedron* **1992**, *48*, 335–340.

(23) Standard free energy values of compound **5d**, calculated at 298.15 K and relative to compound **1d**, are $\Delta G°$ = 15.0 kJ/mol (in vacuo), $\Delta G°$ = 15.4 kJ/mol (in DMSO), and $\Delta G°$ = 13.5 kJ/mol (in MeOH). The standard free energy value calculated at the B3LYP/6-31++G(d,p) level is−572.04948 au for **1d**; the solvation free energy values for **1d** are −4.65 kcal/mol (in DMSO) and −11.92 kcal/mol (in MeOH).

SCHEME 7



1a,**b** were synthesized as previously reported.[10] By following a similar procedure, compounds **1c**,**d** were prepared by acylation of 3-amino-5-methylisoxazole (2.0 g; 20.41 mmol) with a slight excess of the appropriate acyl chloride (22 mmol) in anhydrous toluene containing an equimolar amount of pyridine (22 mmol) at room temperature. After the reaction was completed, the solvent was removed and the residue treated with water, neutralized, and filtered. 3-(4′-Chlorobenzoylamino)-5-methylisoxazole **1c** (4.30 g; 89%): mp 215−216 °C (from toluene); IR (Nujol) 3216, 3151, 1695, 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.46 (s, 3H), 6.90 (s, 1H), 7.48−7.51 (m, 2H), 7.95−7.98 (m, 2H), 9.98 (s, 1H, exchangeable with D_2O); HRMS calcd for $C_{11}H_9ClN_2O_2$ 236.0353, found 236.0351. 3-Isobutyrroylamino-5-methylisoxazole **1d** (3.55 g; 75%): mp 119−120 °C (from light petroleum); IR (Nujol) 3224, 3154, 1704, 1634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.26 (d, 6H, J = 6.9 Hz), 2.41 (s, 3H), 2.67 (hept, 1H, J = 6.9 Hz), 6.78 (s, 1H), 9.80 (bs, 1H, exchangeable with D_2O); HRMS calcd for $C_8H_{12}N_2O_2$ 168.0899, found 168.0902.

Authentic samples of oxadiazoles **5a**,**d** have been prepared accordingly to a procedure reported for oxadiazole **5d**[25] from the reaction of amidoxime **9**[25] with either benzoyl chloride for (**5a**) or isobutyryl chloride (for **5d**) (Scheme 7).

A mixture of amidoxime **9** (2.0 g; 12.5 mmol), pyridine (20 mL), and either benzoyl or isobutyryl chloride (14.0 mmol) was stirred at room temperature overnight. The reaction was then diluted with water and extracted with EtOAc (3 × 150 mL); the combined organic layers were dried on Na_2SO_4 and filtered. After solvent removal, the residue was melted at 130−140 °C for 1 h to thermally promote cyclization into oxadiazoles **11**, which, in turn, were deprotected by stirring at room temperature with 3.3 M HCl (11 mL) for 2 h. The reaction was then diluted with water, neutralized with $NaHCO_3$, and extracted with Et_2O (3 × 150 mL); the combined organic layers were dried on Na_2SO_4 and filtered. After solvent removal, the residue was chromatographed to yield final oxadiazoles **5a**,**d**. 3-Acetonyl-5-phenyl-1,2,4-oxadiazole **5a** (1.10 g; 45%): mp 103−105 °C (from light petroleum/ethyl acetate); IR (Nujol) 1711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.95 (s, 2H), 7.50−7.60 (m, 3H), 8.11−8.13 (m, 2H); HRMS calcd for $C_{11}H_{10}N_2O_2$ 202.0742, found 202.0739. 3-Acetonyl-5-isopropyl-1,2,4-oxadiazole **5d**[25] (1.05 g; 50%): colorless oil; IR (Nujol) 1733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (d, 6H, J = 6.9 Hz), 2.24 (s, 3H), 3.19 (hept, 1H, J = 6.9 Hz), 3.82 (s, 2H); HRMS calcd for $C_8H_{12}N_2O_2$ 168.0899, found 168.0896.

Besides using **5a** as a substrate for analytical scale reactions (see below), samples of **5a** and **5d** were used as reference compounds to facilitate their detection from reaction mixtures containing them in very low concentration.

General Procedure for the Reaction of Compounds 1a−d in DMF/*t*-BuOK. The procedure to perform the base-catalyzed rearrangements of isoxazoles **1a−d** was similar to the one previously reported.[10] A 0.5 g portion of isoxazole was dissolved in 15 mL of DMF and added with 1 equiv of *t*-BuOK. The reaction mixture was then heated at 110 °C and monitored by TLC. After 4 h, the mixture was diluted with water (100 mL), neutralized with acetic acid, and extracted with ethyl acetate. The unified organic layers were dried over Na_2SO_4, filtered, and evaporated and the residue chromatographed.

Reaction of Compound 1a in DMF/*t*-BuOK. Chromatography of the reaction mixture yielded starting material **1a** (0.05 g; 10%) and oxazole **8a** (0.40 g; 80%). Traces of oxadiazole **5a** were detected, by comparison with an authentic sample, on a repeatedly eluted TLC of concentrated chromatographic fractions collected during the elution of isoxazole **1a**. Compound **8a** had mp 133−135 °C (from benzene; lit.[10] mp 134 °C).

Reaction of Compound 1b in DMF/*t*-BuOK. Chromatography of the reaction mixture yielded starting material **1b** (0.08 g; 16%) and oxazole **8b** (0.38 g; 76%). Traces of oxadiazole **5b** (isolated and fully characterized from the reactions under neutral conditions; see later) were detected on a repeatedly eluted TLC of concentrated chromatographic fractions collected during the elution of isoxazole **1b**. Compound **8b** had mp 147−149 °C (from benzene; lit.[10] mp 148−150 °C).

Reaction of Compound 1c in DMF/*t*-BuOK. Chromatography of the reaction mixture yielded starting material **1c** (0.06 g; 12%) and 2-(4′-chlorobenzoylamino)-5-methyloxazole **8c** (0.40 g; 80%). Traces of oxadiazole **5c** (isolated and fully characterized from the reactions under neutral conditions; see later) were detected on a repeatedly eluted TLC of concentrated chromatographic fractions collected during the elution of isoxazole **1c**. Compound **8c**: mp 165−167 °C (from light petroleum/ethyl acetate); IR (Nujol) 3136, 1714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.15 (s, 3H), 6.29 (s, 1H), 7.23 (d, 2H, J = 8.4 Hz), 7.86 (d, 2H, J = 8.4 Hz), 10.74 (Very broad s, 1H exchangeable with D_2O); HRMS calcd for $C_{11}H_9ClN_2O_2$ 236.0353, found 236.0350.

Reaction of Compound 1d in DMF/*t*-BuOK. Chromatography of the reaction mixture yielded starting material **1d** (0.11 g; 22%) and oxazole **8d** (0.37 g; 74%). No traces of oxadiazole **5d**, which was synthesized as reference compound (see above) were detected either during the reaction or in the collected chromatographic fractions. 2-Isobutyrroylamino-5-methyloxazole **8d**: mp 107−109 °C (from light petroleum/ethyl acetate); IR (Nujol) 3169, 3134, 1705, 1674 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 6H, J = 6.9 Hz), 2.33 (s, 3H), 2.72 (broad, 1H), 6.53 (s, 1H), 11.20 (very broad s, 1H, exchangeable with D_2O); HRMS calcd for $C_8H_{12}N_2O_2$ 168.0899, found 168.0897.

Analytical-Scale Reactions of Compounds 1a and 5a in EtOH/*t*-BuOK. Four identical solutions of isoxazole **1a** and of oxadiazole **5a** (0.05 g; 0.247 mmol) in ethanol (20 mL) were prepared. A 1 mL portion of a 0.025 M solution of *t*-BuOK in ethanol was added to each of the above solutions. The eight solutions were then refluxed under identical conditions and the reactions stopped at different times (0.5, 1.0, 2.5, and 4.0 h) by removing the heat source and cooling in a water/ice bath. The solvent was removed at room temperature under reduced pressure and the residue treated with water (50 mL), neutralized, and extracted with diethyl ether (4 × 75 mL). The combined organic layers were dried on Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. In all eight cases, quantitative mass recovery was obtained. The obtained residue was then dissolved in $CDCl_3$ and analyzed by NMR. Amounts of compounds **1a**, **5a**, and **8a** were determined by integration of the methyl signals at 2.43, 2.33, and 2.30 ppm, respectively, and the results are reported in Table 2.

Reaction of Compound 1a in the Absence of Solvent. Isoxazole **1a** (0.6 g; 2.97 mmol) was heated in a sealed tube at 170 °C (at which temperature the reaction occurred in a melted liquid phase) for 4 h. The tube was then allowed to cool at room temperature and the residue chromatographed to yield starting isoxazole **1a** (0.54 g; 90%) and oxadiazole **5a** (0.03 g; 5%).

General Procedure for the Reaction of Compounds 1a−d in Ethylene Glycol. Isoxazoles **1a−d** (0.50 g) were dissolved in ethylene glycol (20 mL), and the mixture was allowed to stir, in a closed tube, at 170 °C for 30 min. The reaction mixture was then

(24) (a) Vivona, N.; Cusmano, G.; Ruccia, M.; Spinelli, D. *J. Heterocycl. Chem.* **1975**, *12*, 985–988. (b) Buscemi, S.; Frenna, V.; Vivona, N.; Petrillo, G.; Spinelli, D. *Tetrahedron* **1995**, *51*, 5133–5142. (c) Buscemi, S.; Frenna, V.; Pace, A.; Vivona, N.; Cosimelli, B.; Spinelli, D. *Eur. J. Org. Chem.* **2002**, 1417–1423.

(25) Kübel, B. *Monatsh. Chem.* **1982**, *113*, 793–803.

cooled to room temperature, diluted with water (100 mL), and extracted with diethyl ether (4 × 100 mL). The combined organic layers were further washed with water, dried on Na_2SO_4, and filtered, and the residue was chromatographed after solvent removal.

Reaction of Compound 1a in Ethylene Glycol. Chromatography of the residue yielded starting isoxazole **1a** (0.31 g; 62%), 3-acetonyl-5-phenyl-1,2,4-oxadiazole **5a**, (0.04 g; 8%), 2-benzoylamino-5-methyloxazole **8a**[10] (0.05 g; 10%), and ethylene glycol monobenzoate (0.03 g; 7%) likely formed by solvolysis of acylamino derivatives **1a** or **8a**.

Reaction of Compound 1b in Ethylene Glycol. Chromatography of the residue yielded starting isoxazole **1b** (0.28 g; 56%), 3-acetonyl-5-(4′-methoxyphenyl)-1,2,4-oxadiazole **5b** (0.03 g; 6%), 2-(4′-methoxybenzoylamino)-5-methyloxazole **8b**[10] (0.03 g; 6%), and ethylene glycol mono(4′-methoxy)benzoate (0.03 g; 7%) likely formed by solvolysis of **1b** or **8b**. Compound **5b**: mp 93−94 °C (from light petroleum/ethyl acetate): IR (Nujol) 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.90 (s, 3H), 3.93 (s, 2H), 7.02 (d, 2H, J = 9.0 Hz), 8.07 (m, 2H, J = 9.0 Hz); HRMS calcd for $C_{12}H_{12}N_2O_3$ 232.0848, found 232.0846.

Reaction of Compound 1c in Ethylene Glycol. Chromatography of the residue yielded starting isoxazole **1c** (0.30 g; 60%), 3-acetonyl-5-(4′-chlorophenyl)-1,2,4-oxadiazole **5c**, (0.07 g; 14%), 2-(4′-chorobenzoylamino)-5-methyloxazole **8c** (0.05 g; 10%), and ethylene glycol mono(4′-chloro)benzoate (0.05 g; 12%) likely formed by solvolysis of **1c** or **8c**. Compound **5c**: mp 120−121 °C (from light petroleum/ethyl acetate); IR (nujol) 1718 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.96 (s, 2H), 7.52 (d, 2H, J = 8.4 Hz), 8.08 (d, 2H, J = 8.4 Hz); HRMS calcd for $C_{11}H_9ClN_2O_2$ 236.0353, found 236.0356.

Reaction of Compound 1d in Ethylene Glycol. Chromatography of the residue yielded starting isoxazole **1d** (0.25 g; 50%), 2-isobutyrylamino-5-methyloxazole **8d** (0.05 g; 10%), and ethylene glycol monoisobutyrate (0.05 g; 13%) likely formed by solvolysis of **1d** or **8d**.

Computational Details. The molecular and anionic species considered, shown in Schemes 3 and 5, were the lowest energy tautomers and/or conformers found for each isomer in the MeOH solvent (see below). Their geometry was fully optimized by using the hybrid DFT B3LYP method[26] and the 6-31++G(d,p) basis set.[27] Their Cartesian coordinates are available in the Supporting Information. Transition-state structures were found by the synchronous transit guided quasi-Newton method.[28] Vibration frequency calculations, within the harmonic approximation, were performed to confirm whether each obtained geometry represented a transition state or a minimum in the potential energy surface. All of the minimum energy structures presented only real vibrational frequencies, whereas all of the transition state structures found were first-order saddle points. To take into account the relative stabilization of intermediates, the standard free energies, at 298.15 K, of the considered species have been evaluated by vibrational frequency calculations of the in vacuo species. Their free energy in DMSO and in MeOH solutions was evaluated by adding the solvation free energy to the free energy of the species in vacuo.[3] The solvation free energy in DMSO and in MeOH was calculated by the conductor-like polarized continuum model,[29] without further optimization of the geometry (i.e., single point calculations) within the solvent medium.

All calculations were performed using the Gaussian98 program package.[30]

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

Supporting Information Available: Comparison table of calculated activation barriers of BK, MNAC, and RCRE rearrangements for some O−N bond containing azole systems. Cartesian coordinates, B3LYP energy (in au), and standard thermochemical data (in au) at 298.15 K of compounds reported in Tables 1 and 3 as well as of compounds **1d** and **5d**. ^1H NMR scpectra of compounds **1c**,**d**, **5a**−**d**, and **8c**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802081K

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