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Novel ring transformation of mesoionic oxazoles into 2(1*H*)-pyrazinones by the reaction with TosMIC ☆

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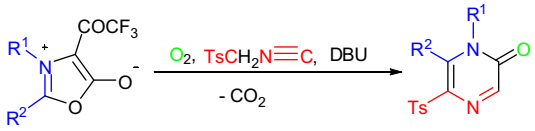
ABSTRACT

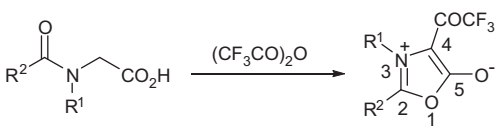
Treatment of mesoionic 1,3-oxazolium-5-olates with TosMIC in the presence of a base causes a novel ring transformation affording 2(1*H*)-pyrazinones in moderate yields. The origin of C-2 carbonyl oxygen in the product was elucidated to be molecular oxygen, based on ^{18}O-labeling experiments.



Ring transformation of heterocyclic compounds is an important area of chemistry from both theoretical and practical viewpoint.[1,2] Such processes may provide interesting synthetic routes to derivatives that are not easily accessible by other methods.

Mesoionic compounds have become useful and versatile synthons en route to varied and functionalized heterocyclic systems.[3] Their reactivity stems from their masked 1,3-dipolar character, thus interacting with a wide range of dipolarophiles in cycloaddition reactions. One useful class of these mesoionic compounds is 1,3-oxazolium-5-olates, commonly known as münchnones.[4] Despite significant interest in these mesoionic heterocycles, their transformation to another ring system via a nucleophilic reaction has received relatively little attention.

Mesoionic 4-trifluoroacetyl-1,3-oxazolium-5-olates (**1**) are easily prepared from *N*-acyl-*N*-alkylglycines (**2**) in a one step through the cyclodehydration by trifluoroacetic anhydride followed by trifluoroacetylation at C-4 position of an intermediary mesoionic 1,3-oxazolium-5-olates (Eq. (1)).[5]



(1)

In principle, the addition of nucleophiles to **1** can a priori be expected to occur at three different positions (C-2, C-5, or $COCF_3$). Previously, we reported that reactions of mesoionic **1** with *N*-nucleophiles such as amidines, ammonia, phenylhydrazine, and aminomalonate proceeded, depending on the nature of the nucleophiles and the reaction conditions.[5] Generally, these reactions occur *via* the initial attack of the *N*-nucleophiles on the C-2 position of the ring. On the other hand, it is shown that *O*-nucleophiles such as H_2O, EtOH, and AcOH attack at C-5 of **1**.[6] Recently, reactions of phosphorus- or sulfur-ylides are found to attack the C-2 position of **1**, affording pyrrole derivatives.[7] *p*-Toluenesulfonylmethyl isocyanide (TosMIC) is a versatile, widely applicable reagent bearing an active methylene group and readily forms a stabilized, nucleophilic carbanion, which will react with a variety of electrophiles, such as aldehydes, ketones, and imines.[8] This class of reagent has most commonly been used in heterocyclic ring construction, in particular, of oxazole, pyrrole, and imidazole moieties.

We report herein a novel type of ring transformation of mesoionic oxazoles **1** into 2(1*H*)-pyrazinones **3** via an initial attack of TosMIC on the C-2 position of the ring.

Table 1 shows the results when 4-trifluoroacetyl-1,3-oxazolium-5-olate (**1a**) was allowed to react with TosMIC in the presence of base. Various sets of reaction conditions were investigated to determine the optimum conditions (Table 1). We found that the order in which the reagents are mixed has a profound effect on the yields. First, the base was added to a solution of **1a** and TosMIC in DMF and the yields were low (Table 1, entries 1–6). However, the better yields were generally obtained by adding the mesoionic compound last to the reaction mixture (Table 1, entries 7–10).

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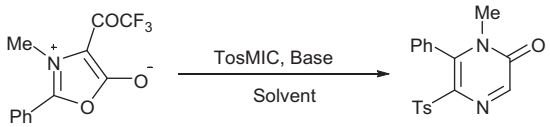
Table 1
Optimization of reaction conditions[a,b]



1a **3a**

Entry	TosMIC (*n* equiv)	Base (*x* equiv)	Solvent	Condition	Yield (%)
1	1.2	K_2CO_3 (2)	Dry MeOH	rt, 19 h	7
2	1.2	*t*BuOK (2)	THF	rt, 17 h	33
3	2.4	*t*BuOK (4)	DMF	0 °C, 3 h	34
4	2.4	*t*BuOK (4)	DMF	−20 °C, 6 h	39
5	1.2	NaH (2)	DMF	rt, 3 h	9
6	1.2	DBU (2)	DMF	rt, 1 h	28
7[c]	1.5	DBU (2)	DMF	0 °C, 2 h	61
8[c]	1.5	MTBD (2)	DMF	0 °C, 2 h	58
9[c]	1.5	*t*BuOK (2)	DMF	0 °C to rt, 5 h	40
10[c]	1.5	P4-*t*Bu (2)	DMF	0 °C to rt, 6 h	67

[a] Reactions were performed with **1a** (1 mmol), TosMIC (*n* equiv), and base (*x* equiv) in solvent (5 mL) under an atmosphere of Ar without any precaution to exclude air in the solvent.
[b] Isolated yields.
[c] **1a** was added after stirring at 0 °C for 1 h.

Table 2
Reaction of **1a** to form **3a**[a,b]

Entry	Condition	Yield (%) of **3a**
1	Under Ar atmosphere (the solvent DMF was degassed by sonication under Ar)	44
2	Under Ar atmosphere[c]	61
3	Under air (using $CaCl_2$ drying tube)	59
4	Under O_2 atmosphere[d]	59
5	Under O_2 atmosphere (with bubbling by O_2 in the solvent through the reaction)	72

[a] A solution of TosMIC (1.5 mmol) and DBU (2 mmol) in DMF (5 mL) was stirred at 0 °C for 1 h, then **1a** (1 mmol) was added to the solution and the reaction mixture was stirred at 0 °C for 3 h.
[b] Isolated yields.
[c] The reaction was performed without any precaution to exclude air in the solvent DMF.
[d] The reaction was not performed with bubbling by O_2.

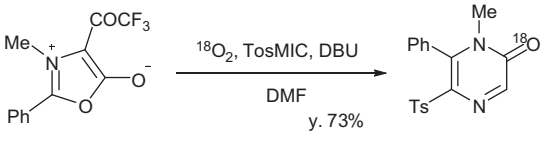
Among the base examined [1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), phosphazene base (P4 base),[9] 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), *t*-BuOK, NaH and K_2CO_3], DBU, and P4 base usually gave best results. DBU was elected as the choice of base for all further reactions due to the cheapness and easy handling.

Next, we investigated the influence of O_2 on the outcome of the reaction (Table 2). The reaction was performed on five kinds of reaction conditions; (1) under Ar atmosphere in the solvent DMF degassed by sonication under Ar, (2) under Ar atmosphere without any precaution to exclude air in the solvent DMF, (3) under air using $CaCl_2$ drying tube for the protection from moisture, (4) under O_2 atmosphere without bubbling by O_2, and (5) under O_2 atmosphere with bubbling by O_2 throughout the reaction. The O_2 present in the solvent was enough for completion of the reaction (entries 2–4). However, the highest yield of product **3a** was obtained when the reaction was done under an atmosphere of O_2 with bubbling by O_2 (entry 5).

With the optimized conditions in hand,[10] the scope of the reaction substrates was investigated. The results are summarized in Table 3, when the reaction was performed under O_2 atmosphere with bubbling by O_2 throughout the reaction. Thus, the substituents on C2 and N3 of the mesoionic ring on the reaction were investigated. The reaction is efficient in both 3-alkyl- and 3-aryl-substituted mesoionic compounds (entries 1–4 and 7–9). However, 2-methyl compounds **1e** gave slightly lower yields compared to 2-aryl-substituted compounds **1a–d** and **f–h**. In this reaction, several polar materials were detected by TLC, but none of them were characterized. In the case of the reaction of **1e**, the yield of **3e** improved from 19% to 42% when the reaction was carried out at −40 °C (entries 5 and 6). To our disappointment, 2-*tert*-butyl-substituted mesoionic compounds **1i** and **j** gave the expected 2-pyrazinones in low yield or not at all (entries 10 and 11), presumably due to the steric hindrance of the *tert*-butyl group at 2-position of **1i** and **j**.

The structure of **3a** was unequivocally confirmed by X-ray diffraction study of single crystals (Fig. 1).[11] The ^{1}H NMR spectrum of **3a** exhibited the signal of 3-H at δ 8.13 and other products (**3b–i**) showed the characteristic 3-H at the same position.

An insight into the pathway of the reaction was sought by conducting the reaction under an atmosphere of $^{18}O_2$. The reaction of **1a** with TosMIC under $^{18}O_2$ atmosphere gave a pyrazinone **3a*** (^{18}O content: 67%) in 73% yield (Eq (2)). Thus, the carbonyl group of amide in compound **3a*** contained more than 67% of the ^{18}O label.[12]

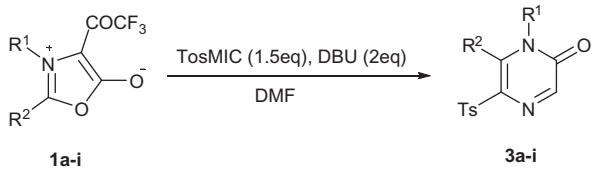


1a **3a***

(2) (2)

A tentative mechanism which accounts for the formation of **3** is depicted in Scheme 1. Thus, initial nucleophilic attack by the TosMIC anion on C-2 of **1** gave rise to an adduct **4** which is converted into the intermediate **5** via proton transfer, which may be in equilibrium with **6**. The driving force for the decarboxylation of **6** is probably due to the electron-donating TosMIC anion and the electron-withdrawing trifluoromethyl ketone. Subsequent ring closure by intramolecular nucleophilic attack of the anion **7** to the electrophilic isocyano carbon may afford **8** which undergoes proton transfer to give **9**. Intermediate **9** would be the electron donor to O_2. Thus, formation of free radical-superoxide complex **10**, followed

Table 3
2(1*H*)-Pyrazinones from various mesoionic oxazoles and TosMIC[a,b]



Entry	**1**	R^1	R^2	Condition	Product	Yield (%)
1	**a**	Me	Ph	0 °C, 3 h	**3a**	72
2	**b**	Me	4-BrC_6H_4	0 °C, 5 h	**3b**	70
3	**c**	Me	4-$MeOC_6H_4$	0 °C, 1 h	**3c**	78
4	**d**	Ph	Ph	0 °C, 4 h to rt, 19 h	**3d**	65
5	**e**	Ph	Me	0 °C, 4 h to rt, 18 h	**3e**	19
6	**e**	Ph	Me	−40 °C, 12 h	**3e**	42
7	**f**	$PhCH_2$	Ph	0 °C, 4.5 h	**3f**	55
8	**g**	4-$MeOC_6H_4CH_2$	Ph	0 °C, 5 h	**3 g**	53
9	**h**	$PhCH_2$	4-$MeOC_6H_4$	0 °C, 5 h	**3 h**	58
10	**i**	Me	*t*Bu	0 °C, 3 h	**3i**	11
11	**j**	Ph	*t*Bu	0 °C, 4.5 h	**3j**	0

[a] A solution of TosMIC (1.5 mmol) and DBU (2 mmol) in DMF (5 mL) was stirred at 0 °C for 1 h, then **1** (1 mmol) was added to the solution under an atmosphere of O_2 with bubbling of O_2 throughout the reaction.
[b] Isolated yields.

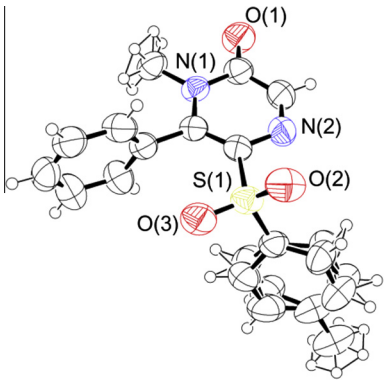
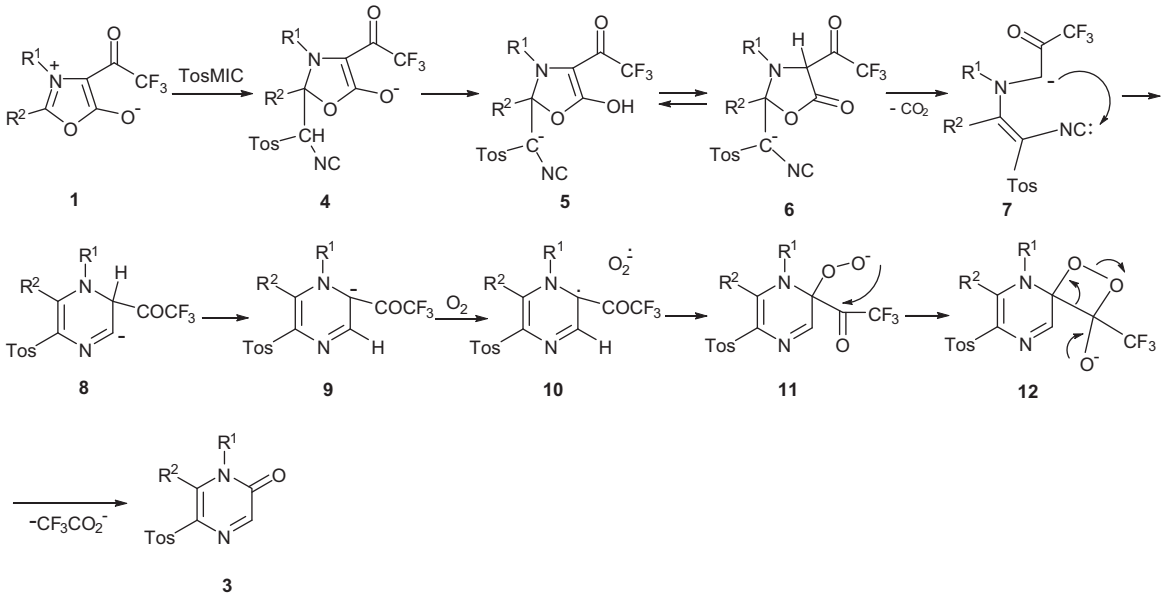


Figure 1. X-ray structure drawing of **3a**.

by recombination of superoxide with the incipient carbon free radical, might produce hydroperoxide anion **11**. This anion **11** leads to the intermediate **12** which extrudes trifluoroacetate anion to provide the 2-pyrazinone **3**.

In conclusion, starting from the mesoionic **1** and TosMIC, a new and efficient synthesis of 1,6-disubstituted 5-tosyl-2(1*H*)-pyrazinones has been described. The 2(1*H*)-pyrazinone is an important privileged scaffold in medicinal chemistry, as well as in several alkaloids with diverse biological activity, including antitumor and antiviral properties.[14] Therefore, several methods for the synthesis of 2(1*H*)-pyrazinones have been described in the literature: (a) condensation of α-aminoamides with α-diketones,[15] (b) condensation of α-aminonitrile with oxalyl halides,[14c,16] and (c) Ugi four-component reactions.[17] Whereas these methods have proven very useful for the synthesis of 2(1*H*)-pyrazinones, they generally involve multistep synthetic operations and/or a hazardous cyanide



Scheme 1. Proposed mechanistic pathway.

source that limit the scope of these reactions. Indeed, it is still desirable to develop an efficient method for the synthesis of 2(1*H*)-pyrazinones. The present reaction could proceed *via* an initial attack of TosMIC anions on the C-2 position of the ring, opening of the oxazole ring, subsequent cyclization, and autoxidation, which includes oxygenation, cyclization of the resulting peroxy anion, and oxidative cleavage. This unique ring transformation reaction of mesoionic oxazoles with TosMIC was not anticipated but the reaction is general as evidenced by the examples indicated in Table 3. The method appears to be useful and convenient in terms of the ready accessibility of the starting materials, operational simplicity, and mild condition.

Acknowledgement

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References and notes

1. Hajos, G.; Riedl, Z.; Kollenz, G. *Eur. J. Org. Chem.* **2001**, 3405.
2. Van der Plas, H. C. In *Ring Transformation of Heterocycles*; Academic Press: New York, 1973; Vols. 1 and 2,
3. Gribble, G. W. Mesoionic Ring Systems In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; John Wiley & Sons: Hoboken, 2002; Vol. 59, p 681. Chapter 10.
4. Gribble, G. W. Mesoionic Oxazoles In *The Chemistry of Heterocyclic Compounds Oxazoles: Synthesis, Reactions, and Spectroscopy Part A*; Taylor, E. C., Wipf, P., Eds.; John Wiley & Sons: Hoboken, 2003; Vol. 60, p 473.
5. (a) Kawase, M.; Koiwai, H. *Chem. Pharm. Bull.* **2008**, *56*, 433; (b) Kawase, M.; Saito, S.; Kurihara, T. *Chem. Pharm. Bull.* **2001**, *49*, 461; (c) Kawase, M.; Saito, S. *Chem. Pharm. Bull.* **2000**, *48*, 410.
6. Kawase, M.; Koiwai, H.; Kurihara, T. *Tetrahedron Lett.* **1998**, *39*, 6189.
7. (a) Saijo, R.; Hagimoto, Y.; Kawase, M. *Org. Lett.* **2010**, *12*, 4776; (b) Saijo, R.; Kawase, M. *Tetrahedron Lett.* **2012**, *53*, 2782.
8. Van Leusen, D.; Van Leusen, A. M. *Org. React.* **2001**, *57*, 417.
9. P4 base is 1-*tert*-butyl-4,4,4-tris(dimethylamino)-2,2-bis[tris(dimethylamino)-phosphoranylidenamido]- $2\lambda^5,4\lambda^5$-catenadi(phosphazene).
10. *General procedure for the reactions of* ***1*** *with TosMIC:* To a stirred solution of TosMIC (293 mg, 1.50 mmol) in DMF (5 mL) was added DBU (304 mg, 2.00 mmol) at 0 °C, and the mixture was stirred for 1 h under an atmosphere of O_2. To the mixture was added 4-trifluoroacetyl-1,3-oxazolium-5-olate **1** (1.00 mmol) with bubbling of O_2 throughout the reaction and the whole was stirred at 0 °C for an additional several hours. After workup with water, the mixture was extracted with AcOEt (×3). The combined organic layers were washed with brine, dried over anhyd Na_2SO_4, and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt = 4:1 to 1:1) to give product **3**.
1-Methyl-6-phenyl-5-tosylpyrazin-2(1*H*)-one (**3a**): Mp 147−149 °C ($CHCl_3$–hexane); IR (KBr) ν_{max} 3057, 1674, 1662, 1487, 1322, 575 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 2.41 (s, 3H, ArCH_3), 3.13 (s, 3H, NCH_3), 7.21–7.27 (m, 4H, Ar*H*), 7.51–7.59 (m, 5H, Ar*H*), 8.13 (s, 1H, *H*-3); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 21.5, 33.3, 128.3, 128.6, 128.9, 129.0, 129.4, 130.6, 134.0, 137.3, 144.3, 145.0, 145.8, 155.5. MS *m*/*z*: 410 (M^+, 5.1), 118 (100). Anal. Calcd for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.32; H, 5.03; N, 8.09.
11. The structure of **3a** was confirmed by X-ray analysis (CCDC no. 832512). The tosyl moiety is disordered and the ratio is calculated to be 0.674:0.326.
12. The ^{13}C NMR spectrum indicated that ^{18}O had been incorporated on the carbonyl carbon of amide, based on the observation of ^{18}O-isotope effect[13] on the chemical shift of the carbonyl carbon. MS and IR data also supported this structure.
13. Vederas, J. C. *Chem. Soc.* **1980**, *102*, 374.
14. (a) Mehta, V. P.; Sharma, A. K.; Modha, S. G.; Sharma, S.; Meganathan, T.; Parmar, V. S.; Van der Eycken, E. *J. Org. Chem.* **2011**, *76*, 2920; (b) Ortqvist, P.; Gising, J.; Ehrenberg, A. E.; Vema, A.; Borg, A.; Karlen, A.; Larhed, M.; Danielson, U. H.; Sandstrom, A. *Bioorg. Med. Chem.* **2010**, *18*, 6512; (c) Pawar, V. G.; De Borggraeve, U. H. *Synthesis* **2006**, *17*, 2799.
15. (a) Tota, Y. A.; Elderfield, R. C. *J. Org. Chem.* **1942**, *7*, 313; (b) Karmas, G.; Spoerri, P. E. *J. Am. Chem. Soc.* **1952**, *74*, 1580.
16. (a) Vekemans, J.; Pollers-Wieers, C.; Hoornaert, G. J. *J. Heterocycl. Chem.* **1983**, *20*, 919; (b) Gising, J.; Ortqvist, P.; Sandstrom, A.; Larhed, M. *Org. Biomol. Chem.* **2009**, *7*, 2809.
17. Azuaje, J.; El Maatougui, A.; Perez-Rubio, J. M.; Coelho, A.; Fernandez, F.; Sotelo, E. *J. Org. Chem.* **2013**, *78*, 4402.