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Reaction of quinoxalin-2-ones with TosMIC reagent: synthesis of imidazo[1,5-*a*]quinoxalin-4-ones

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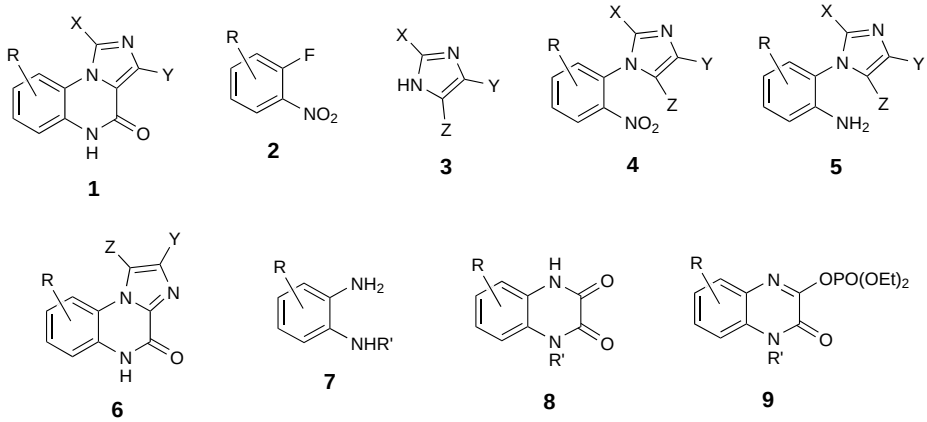
Abstract—Imidazo[1,5-*a*]quinoxalin-4-ones were prepared in four steps starting from 1,2-phenylenediamines using a new strategy for the construction of the ring system. A key step in this new method involves the reaction of quinoxalin-2-ones with TosMIC (tosylmethyl isocyanide).

Imidazo[1,5-*a*]quinoxalin-4-ones are common structural arrays that are found in a variety of biologically important and medicinally useful agents and therefore often serve as important intermediates for their synthesis. For example, they have been used as templates for the synthesis of GABA/benzodiazepine receptor agonists/antagonists,[1] cAMP and cGMP phosphodiesterase inhibitors,[2] A_1- and A_{2a}-adenosine receptor agonists[3] in addition to many other pharmacologically active compounds.[4–7] Three methods have been previously developed for the preparation of imidazo[1,5-*a*]-quinoxalin-4-ones. The first method involved the coupling of 2-fluoronitrobenzenes **2** with imidazoles (**3**, X≠H, Z=H) via nucleophilic aromatic substitution to give 1-(2-nitrophenyl)imidazoles (**4**, X≠H, Z=H).[2–4,8] Reduction of **4** (X≠H, Z=H) afforded the corresponding 2-imidazolylanilines **5** (X≠H, Z=H), which upon reaction with carbonyldiimidazole gave rise to imidazo[1,5-*a*]-quinoxalin-4-ones. While this approach is quite useful for the synthesis of 1-substituted imidazo[1,5-*a*]-quinoxalin-4-ones (**1**, X≠H),[2–4] it is not adaptable to the preparation of 1-unsubstituted imidazo[1,5-*a*]quinoxalin-4-ones (**1**, X=H) since the use of 2-unsubstituted imidazoles (**3**, X=H) in this sequence will ultimately lead to exclusive formation of the isomeric imidazo[1,2-*a*]quinoxalin-6-ones **6**.[2–4,8] The second approach involves the reaction of ethyl imidazole-4,5-dicarboxylate (**3**, Y=Z=COOEt) with 2-fluronitrobenzene to give 1-(2-nitrophenyl)imidazole-4,5-dicarboxylate (**4**, Y=Z=COOEt).[7] Subsequent reduction and spontaneous cyclization of the corresponding aniline (**5**, Y=Z=COOEt) afforded ethoxycarbonyl-imidazo[1,5-*a*]quinoxalin-4-ones **1** (Y=COOEt).[7] In the third method, 1,2-phenylenediamines **7** were condensed with ethyl oxalyl chloride to give 2,3-dioxoquinoxalines **8**, which, after transformation to enol phosphates **9** and subsequent reaction with aryl isocyanides, afforded 3-aryl-imidazo[1,5-*a*]quinoxalin-4-ones (**1**, X=H, Y=



1 **2** **3** **4** **5**

6 **7** **8** **9**

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Ar).[1,5,6] A variety of 1- and/or 3-substituted imidazo[1,5-*a*]-quinoxalin-4-ones have been prepared by appropriate choice of the above methods. These approaches, however, could not be used for the synthesis of both 1- and 3-unsubstituted imidazo[1,5-*a*]-quinoxalin-4-ones (**1**, X=Y=H). Recently, in one of our drug discovery programs, we required easy access to various 1- and 3-unsubstituted imidazo[1,5-*a*]-quinoxalin-4-ones (**1**, X=Y=H). We report herein a novel method for the preparation of these compounds.

Our approach to both 1- and 3-unsubstituted imidazo[1,5-*a*]quinoxalin-4-ones began with the condensation of 1,2-phenylenediamines **10** with ethyl glyoxalate **11** (Scheme 1). Thus, refluxing 1,2-phenylenediamine **10a** and ethyl glyoxalate **11** in ethanol gave quinoxalin-2(1*H*)-one **12a** in 88% yield.[9,10] Treatment of **12a** with sodium hydride in DMF followed by addition of *p*-methoxybenzyl chloride afforded a mixture of *N*-(*p*-methoxybenzyl)-quinoxlin-2-one **13a** and 2-(*p*-methoxybenzyloxy)quinoxline **13′a**. The major isomer **13a** can be isolated by chromatography in 74% yield.[10,11] Reaction of **13a** with TosMIC (tosylmethyl isocyanide) in THF in the presence of a base such as NaH provided 5-(*p*-methoxybenzyl)-imidazo[1,5-*a*]-quinoxalin-4-one **14a** in 97% yield.[10,12] It should be noted that the minor isomer **13′a** reacts very sluggishly with TosMIC to give the corresponding imidazole derivative under similar reaction conditions. Finally, deprotection of the *N*-(*p*-methoxybenzyl) group of **14a** afforded imidazo[1,5-*a*]quinoxalin-4-one **15a** in 97% yield.[10,13] Other imidazo[1,5-*a*]quinoxalin-4-ones were prepared in an analogous manner; these results are summarized in Table 1.

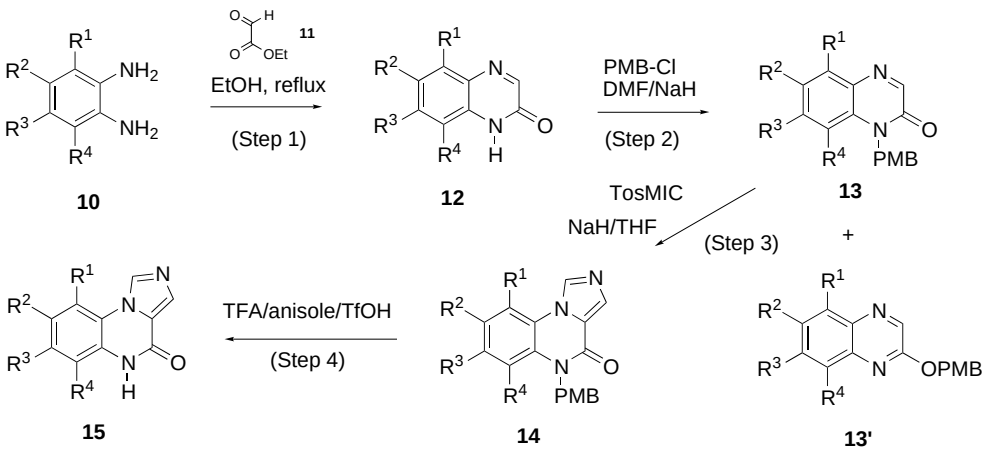
As can been seen from Table 1, this newly developed method is general for the preparation of 1- and 3-unsubstituted imidazo[1,5-*a*]quinoxalin-4-ones with either electron-donating or electron-withdrawing groups on the phenyl ring (Table 1, entries 2 and 3 and entries 4 and 5, respectively). One drawback with this method is the formation of a mixture of quinoxalin-2-one regioisomers when an unsymmetrical phenylenediamine is used, thereby significantly reducing the overall yield (Table 1, entries 4 and 5). However, the desired isomer of intermediate **12** can be prepared regiospecifically via an alternative route if needed (Table 1, entry 2).[14]

Table 1. Preparation of imidazo[1,5-*a*]quinoxalin-4-ones **15**

Entry	R^1	R^2	R^3	R^4	Yield (%)[c]			
					12	**13**	**14**	**15**
1	H	H	H	H	[a]	63	97	97
2	H	H	OMe	H	[b]	61	90	90
3	H	OMe	OMe	H	86	54	96	99
4	H	H	CO_2Me	H	93[d]	67[d]	88[d]	94[d]
5	NO_2	H	H	H	37[e]	70	68	91

[a] Commercially available materials.
[b] For details, see Ref. 14.
[c] Isolated by chromatography unless otherwise indicated.
[d] Isolated as a mixture of regioisomers.
[e] Isolated by crystallization.

In summary, a novel method has been developed for the preparation of both 1- and 3-unsubstituted imidazo[1,5-*a*]quinoxalin-4-ones. A key step in this newly developed method involves an efficient imidazole ring formation by reaction of quinoxalin-2-ones with TosMIC. The application of this new synthetic sequence to the preparation of novel protein tyrosine kinase (PTK) inhibitors will be reported in due course.[15]

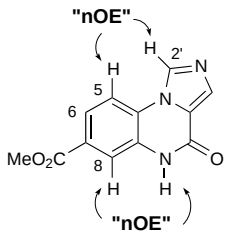


a, $R^1=R^2=R^3=R^4=H$; **b**, $R^1=R^2=R^4=H$, $R^3=OMe$; **c**, $R^1=R^4=H$, $R^2=R^3=OMe$
d, $R^1=R^2=R^4=H$, $R^3=CO_2Me$; **e**, $R^1=NO_2$, $R^2=R^3=R^4=H$

Scheme 1.

References

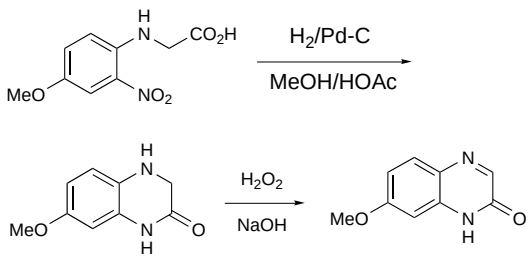
1. Jacobsen, E. J.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 3820.
2. Davey, D. D.; Erhardt, P. W.; Cantor, E. H.; Greenberg, S. S.; Ingebretsen, W. R.; Wiggins, J. *J. Med. Chem.* **1991**, *34*, 2671.
3. Colltta, V.; Cecchi, L.; Catarzi, D.; Filacchioni, G.; Martini, C.; Tacchi, P.; Lucacchini, A. *Eur. J. Med. Chem.* **1995**, *30*, 133.
4. Ohmori, J.; Shimizu-Sasamata, M.; Okada, M.; Sakamoto, S. *J. Med. Chem.* **1997**, *40*, 2053.
5. TenBrink, R. E.; Jacobsen, E. J.; Gammill, R. B. US Patent 5541324, July 30, 1996; *Chem. Abstr.* **1996**, *125*, 195687.
6. Hansen, H. C.; Watjen, F. EP 344943 A1, December 6, 1989; *Chem. Abstr.* **1990**, *112*, 216962.
7. Lee, T. D.; Brown, R. E. US 4440929, April 3, 1984; *Chem. Abstr.* **1984**, *101*, 7202.
8. Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Valle, D. F.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362.
9. (a) Gowenlock, A. H.; Newbold, G. T.; Spring, F. S. *J. Chem. Soc.* **1945**, 622; (b) Collins, P. A.; McFarlane, M. D.; Mackie, R. K.; Smith, D. M. *Tetrahedron* **1992**, *48*, 7887; (c) Epperson, J. R.; Hewawasam, P.; Meanwell, N. A.; Boissard, C. G.; Gribkoff, V. K.; Post-Munson, D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2801.
10. The structures of new intermediates and final products referred to in this work were determined by a combination of spectroscopic techniques (^{1}H and ^{13}C NMR, EI MS) and microanalysis. In particular, the structures of compounds **12d**, **13d** and **14d** were inferred by NOE studies on **15d** (i.e. irradiation of $H_{2'}$ and H_8, respectively, generated NOE signals for corresponding H_5 and N–H and vice versa).



15d

Typical reaction conditions: (a) **13a**: To a 0°C suspension of NaH (11.0 mmol) in 5 mL of dry DMF was added a solution of 2-hydroxyquinoline (10.0 mmol) in 10 mL of dry DMF. After 20 min, *p*-methoxybenzyl bromide (11.0 mmol) was added and the mixture was stirred at ambient temperature for 12 h. The mixture was poured into a mixture of water and EtOAc. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. Flash chromatography then yielded **13a** as a white solid. (b) **14a**: To a 0°C suspension of NaH (1.0 mmol) in dry THF was added a mixture of **13a** (0.5 mmol) and TosMIC (0.5 mmol) in dry THF. The mixture was stirred at room temperature for 4 h and poured into ice water. The white precipitate was collected by filtration, washed with water and dried under high vacuum to give **14a** as a white solid. (c) **15a**: To a mixture of **14a** (1.0 mmol) in 5 mL of TFA and 2 mL of anisole was added 1 mL of triflic acid. The mixture was stirred at room temperature for 6–8 h. After concentration under reduced pressure, the residue was poured into a mixture of ice/saturated $NaHCO_3$–ether with vigorous stirring (final pH >7.0). The white precipitate was collected by filtration, rinsed with water, and triturated with ether to give **15a** as a white solid.

11. For a recent reference on *N*-alkylations of quinoxalin-2-ones, see: Katoh, A.; Yoshida, T.; Ohkanda, J.; Nishio, T. *Heterocycles* **1997**, *44*, 357.
12. For a recent reference on the preparation of imidazoles using TosMIC reagent, see: Chen, B.-C.; Bednarz, M. S.; Zhao, R.; Sundeen, J. E.; Chen, P.; Shen, Z.; Skoumbourdis, A. P.; Barrish, J. C. *Tetrahedron Lett.* **2000**, *41*, 5453.
13. For a recent reference related to deprotection of PMP group on nitrogen using TFA/anisole, see: Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128.
14. Compound **12b** was regiospecifically prepared as shown below:



12b

77% for two steps

For an alternative approach, see: Sakata, G.; Makino, K.; Morimoto, K. *Heterocycles* **1985**, *23*, 143.

15. Barrish, J.; Chen, P.; Das, J.; Iwanowicz, E.; Norris, D.; Padmanabha, R.; Roberge, J.; Schieven, G. Imidazoquinoxaline Protein Tyrosine Kinase Inhibitors, *PCT Int. Appl.* (**1999**), WO 9909845.