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Synthesis of imidazo[1,5-*a*]quinoxalin-4(5*H*)-one template via a novel intramolecular cyclization process

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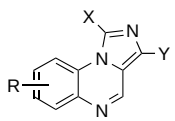
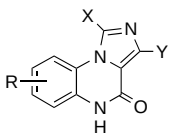
Abstract—A novel, efficient, and regiospecific method for the construction of the imidazo[1,5-*a*]quinoxalin-4(5*H*)-one template is described. The key reaction involves an intramolecular cyclization process and provides the desired products in excellent yield.

Imidazoquinoxalines **1** and the structurally related imidazoquinoxalinones **2** belong to an important class of heterocycles that are often found in biologically active and medicinally useful agents.[1–7] Since imidazo-quinoxalines can often be derived from the corresponding imidazoquinoxalinones, development of an efficient synthesis of the latter is always desirable and of interest to medicinal chemists. In connection with our protein tyrosine kinase (PTK) inhibitor program, we required quick and easy access to various 1- and 3-unsubstituted imidazo[1,5-*a*]quinoxaline-4(5*H*)-ones **2** (where X = Y = H). While there are several methods in the literature describing the synthesis of 1- and/or 3-substituted imidazo[1,5-*a*]quinoxalin-4(5*H*)-ones **2**[1–8] (X ≠ H and/or Y ≠ H), none of these were suitable for our purpose. For example, treatment of 2-(1*H*-imidazol-1-yl)-aniline **3** (X = Y = H) with carbonyldiimidazole (CDI) gives exclusively the undesired imidazo[1,2-*a*]quinoxaline-5(6*H*)-one **4**; whereas the desired isomeric imidazo[1,5-*a*]quinoxalin-4(5*H*)-one **2** (X = H) can only be obtained when the 4-position of the imidazole ring is substituted (X ≠ H).[2] We report herein a novel approach to the efficient synthesis of various substituted 1- and 3-unsubstituted imidazo[1,5-*a*]-quinoxalin-4(5*H*)-ones **2** (X = Y = H) in good to excellent overall yield.

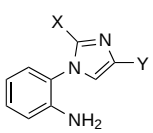
Commercially available 2-fluoroaniline **5a** was acylated in the presence of sodium bis(trimethylsilyl)-amide (NaHMDS) with carbonyl–imidazole dimer **6**[9] to give amide **7a** in 77% yield (Scheme 1). Attempts to directly couple **5a** with 2-imidazocarboxylic acid under standard conditions resulted in the formation of various undesired side-products. Treatment of **7a** with K_2CO_3 in refluxing *N*,*N*-dimethyl-acetamide (DMA) yielded the desired imidazo[1,5-*a*]quinoxalin-4(5*H*)-one **8a** in 73% isolated yield.[10] Other imidazo[1,5-*a*]quinoxaline-



1: imidazo[1,5a]quinoxaline



2: imidazo[1,5a]quinoxalin-4(5H)-one



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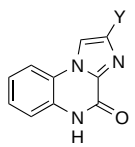

4: imidazo[1,2a]quinoxalin-6(5H)-one

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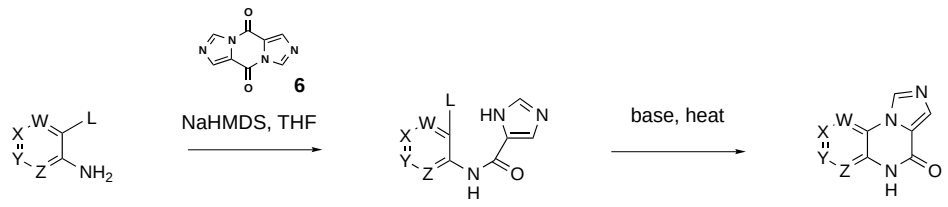


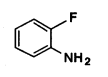
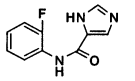
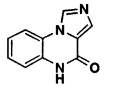
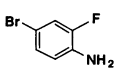
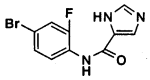
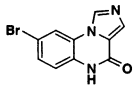
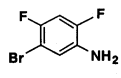
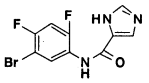
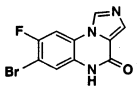
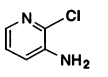
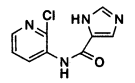
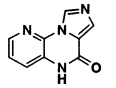
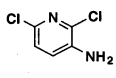
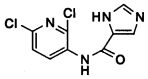
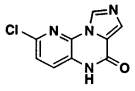
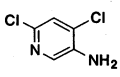
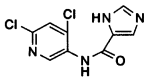
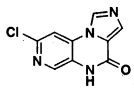
a. W = X = Y = Z = C-H, L = F; **b**. W = Y = Z = C-H, X = C-Br, L = F;
c. W = Z = C-H, X = C-Br, Y = C-F, L = F; **d**. W = N, X = Y = Z = C-H, L = Cl;
e. W = N, X = C-Cl, Y = Z = C-H, L = Cl; **f**. W = Z = C-H, X = C-Cl, Y = N, L = Cl;

Scheme 1.

4(5*H*)-ones were similarly prepared; the results are summarized in Table 1.

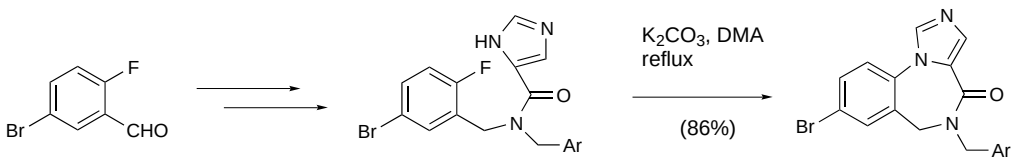
As shown in Table 1, this approach is general and efficient for the preparation of various 1- and 3-unsubstituted imidazo[1,5-*a*]quinoxalin-4(5*H*)-ones **2** (X = Y = H) and provides the desired products in good to excellent overall yields. In addition, this method allows for the preparation of heteroaryl imidazo-[1,5-*a*]-quinoxalin-4(5*H*)-one analogs (entries 4–6). For example, 2-chloro-3-amino-pyridine **5d** can be easily converted to the imidazo[1,5-*a*]-pyrido[2,3-*e*]pyrazin-6(5*H*)-one **8d** using this method (entry 4). Furthermore, this method can be extended to the preparation of imidazo[1,5-*a*][1,4]benzodiazepines **11**, which serve as seven-membered ring templates. Thus, treatment of compound **10** (derived from benzaldehyde **9** in two steps via 1) reductive amination; and 2) acylation with

Table 1. Preparation of imidazo[1,5-*a*]quinoxalin-4(5*H*)-ones **8**

Entry	Compound 5	Compound 7	Yield (%)[a]	Compound 8	Conditions[b]	Yield (%)[a]
1	 5a		77		A	73
2	 5b		76		A	79
3	 5c		93		A	94
4	 5d		40		A	83
5	 5e		96		A	89
6	 5f		77		B	99

[a]Isolated yields; All new compounds give satisfactory spectroscopic data (NMR, LC-MS etc.)[5]

[b]Reaction conditions: Condition A: K_2CO_3, DMA, reflux; Condition B: DBU, DMF, 150-160C.



Scheme 2.

carbonyl–imidazole dimer **6**) under similar conditions yielded compound **11** (Ar = 2,4-dimethoxyphenyl) in 86% isolated yield (Scheme 2).

Typical reaction conditions:

Compound **7d**: To a cold (−10°C) solution of 3-amino-2-chloropyridine (2.87 g, 22.3 mmol) in dry THF (13 mL) purged with argon was added NaHMDS (51 mL, 51 mmol, 1.0 M solution in THF). After 1 h, a suspension of imidazole carbonyl dimer **6** (2 g, 10.6 mmol) in dry THF (20 mL) was added and the reaction mixture was stirred at room temperature for 2 h (or until the reaction was complete as indicated by HPLC). After cooling to 0°C, sufficient acetic acid was added to adjust the pH to ~7 and the mixture was concentrated in vacuo. Water was added, followed by satd $NaHCO_3$. The solid product was collected by filtration, washed with water and hexane, and dried under vacuum to give compound **7d** as a light beige solid.

Compound **8d**: A mixture of compound **7d** (1.89 g, 8.49 mmol) and potassium carbonate (3.5 g, 25.5 mmol) in 40 mL of *N*,*N*-dimethyl acetamide was heated to reflux for 6 h (or until the completion of the reaction as indicated by HPLC or TLC). After cooling to room temperature, the solvent was removed under reduced pressure and water was added, followed by satd NH_4Cl solution. The white precipitate was collected by filtration, rinsed with water and ether, dried under vacuum to give the desired compound **8d** with >95% purity by HPLC. Alternatively, soluble base DBU in DMF can be used in place of potassium carbonate in DMA for the preparation of compound **8** (entry 6, Table 1). In this case, the reaction was completed within 1 h at 160°C (3.0 equiv. DBU).

In summary, we have developed a novel and efficient approach for the construction of imidazo-[1,5-*a*]-quinoxalin-4(5*H*)-one templet. This newly developed method is general and provides products in good to excellent yields. Because the formation of the heterocyclic core via this route is regiospecific, this method serves as a complementary approach to our recently described method using TosMIC reagent that gives both possible regioisomers.[11]

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10. Spectroscopic and analytical data of all new compounds were consistent with their assigned structures. Representative ^1H NMR (400 MHz) data: **8a**: (DMSO-d_6): 9.06 (s, 1H), 8.19 (d, J = 7.62, 1H), 7.87 (s, 1H), 7.15–7.50 (m, 3H); **8b**: (DMSO-d_6): 11.5 (bs, 1H), 9.10 (s, 1H), 8.50 (d, J = 2.13, 1H), 7.87 (d, J = 0.86 Hz, 1H), 7.54 (dd, J = 2.13, J = 8.55, 1H), 7.25 (d, J = 8.55, 1H); **8c**: (DMSO-d_6): 9.00 (s, 1H), 8.37 (d, J = 9.23, 1H), 7.83 (s, 1H), 7.54 (d, J = 6.59, 1H); **8d**: (DMSO-d_6): 11.77 (bs, 1H), 9.35 (s, 1H), 8.30 (dd, J = 1.32, J = 4.83, 1H), 8.18 (s, 1H), 7.77 (dd, J = 1.32, J = 7.91, 1H), 7.55 (dd, J = 4.83, J = 7.91, 1H); **8e**: (DMSO-d_6): 8.87 (s, 1H), 7.93 (s, 1H), 7.71 (d, J = 8.34, 1H), 7.56 (d, J = 8.34, 1H); **8f**: (CD_3OD): 9.02 (s, 1H), 8.37 (s, 1H), 8.25 (s, 1H), 7.99 (s, 1H); **10**: ($CDCl_3$): 7.88 (s, 1H), 7.50 (dd, J = 8.44, J = 2.20, 1H), 7.24 (d, J = 8.44, 1H), 7.19 (d, J = 8.25, 1H), 6.71 (d, J = 2.20, 1H), 6.48, dd, J = 8.25, J = 2.20, 1H), 6.37 (d, J = 2.20, 1H), 4.05–4.25 (m, 2H), 3.85 (s, 3H), 3.58 (s, 3H); **11**: (DMSO-d_6): 8.58 (t, J = 5.16, 1H), 8.49 (s, 1H), 7.83 (s, 1H), 7.74 (dd, J = 8.49, J = 1.68, 1H), 7.66 (dd, J = 8.49, J = 1.68, 1H), 7.65 (s, 1H), 4.14 (d, J = 5.16, 2H).
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