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Efficient synthesis of 2-imidazol-2-ylacetates

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Abstract—A simple method of synthesizing various 2-imidazol-2-ylacetates is described. Condensation of α-aminoketals with imidates, followed by cyclization in refluxing 4 M-HCl/Dioxane, yielded 2-imidazol-2-ylacetates under one-pot and mild reaction conditions.
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Imidazoles frequently are found in biologically active natural products or pharmaceutically important drugs.[1] Our interest in the search for new receptor tyrosine kinase inhibitors[2] has been focusing on the synthesis of 2-quinolinone core derivatives **5** with C-3 imidazole moiety (Fig. 1). The quinolin-2(1*H*)-one-3-imidazoles **5** were readily prepared by condensing 2-imidazol-2-ylacetate **3** with various substituted 2-aminobenzaldehydes **4**.[3] Several methods for the synthesis of 2-imidazol-2-ylacetate derivatives have been described in the literature, which are mainly based on the elaboration of acetate functionality from the simple imidazole derivatives[4–6] or the condensation of ethylenediamine derivatives with imidate followed by dehydrogenation.[7] However the existing methods suffer in terms of moderate yields and availability of starting material with various functional groups. Also, their preparations are difficult in many cases and took many reaction steps. Thus, we decided to investigate the synthesis of imidazoles by condensation of α-aminoketals with imidates developed by Lawson.[8] Whereas numerous syntheses of substituted imidazoles by this method are described in the literature,[9] no synthetic study for 2-imidazol-2-ylacetates has been reported.

Generally, the reaction of imidates and α-aminoketal yields amidine intermediates, which are then cyclized, by heating in aqueous hydrochloric acid solution, to produce imidazoles.[10] However, this approach suffers from the hydrolysis of the ester group that resulted in low product yields. To overcome this problem, we tested the cyclization reaction under a non-aqueous solvent system without isolation of the amidine. In this letter, we disclose our results for a mild and convenient method to synthesize 2-imidazol-2-ylacetate from imidate salt and various α-aminoketal derivatives.

The preparation of various α-aminoketal derivatives from ketones was carried out following the general route via Neber rearrangement procedure,[11] which consists of

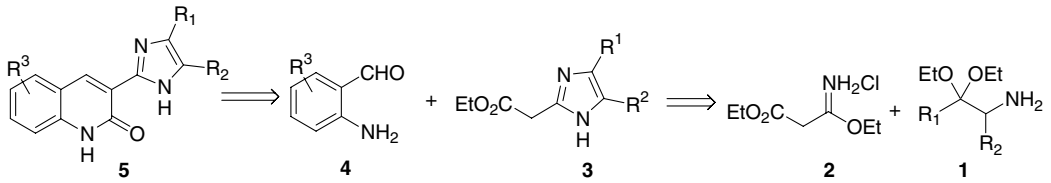

Figure 1. Synthetic approach to 2-imidazol-2-ylacetate.

Keywords: 2-Imidazol-2-ylacetates; α-Aminoketals; Neber rearrangement.
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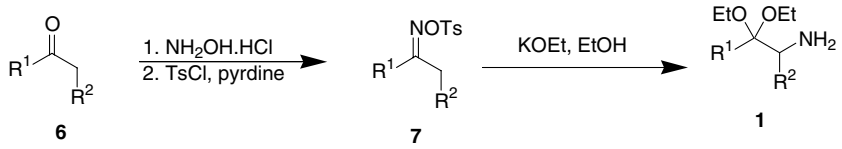
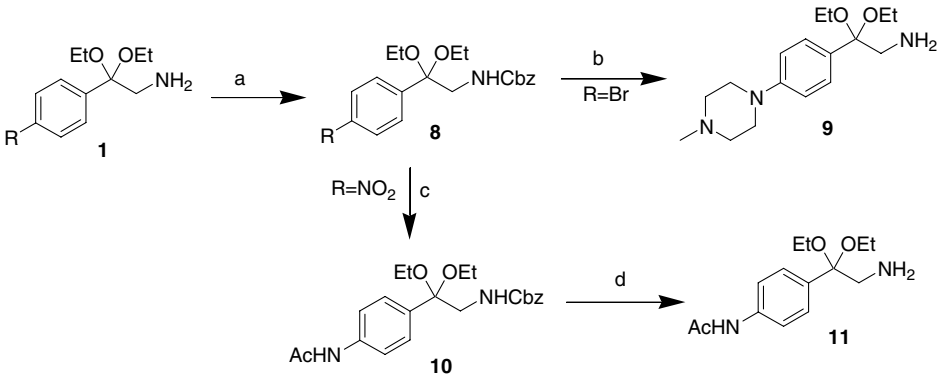


Scheme 1. Synthesis of α-aminoketals via a Neber rearrangement.



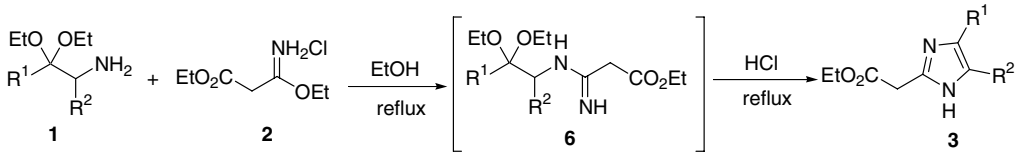
Scheme 2. Reagents and conditions: (a) CbzCl, Et_3N/CH_2Cl_2, 0 °C, 90%; (b) 2-(*t*-BuP)$_2$biphenyl, $Pd_2(dba)_3$, NaO*t*-Bu, *N*-methylpiperazine, toluene, reflux, 92%; (c) (i) Fe, NH_4Cl/EtOH–H_2O, reflux, (ii) AcCl, Et_3N/CH_2Cl_2, 0 °C, 58%; (d) 10% Pd/C, H_2, EtOH, 88%.

the introduction of an amino group at the α-position of a ketone. As shown in Scheme 1, α-aminoketal derivatives **1** were prepared by a KOEt treatment of oxyme tosylate **7**, which was obtained by reacting various ketones **6** with hydroxylamine followed by tosylation of the corresponding oxyme.

Neber rearrangement of the oxyme tosylates with electron-rich aryl groups proved to be problematic, owing to the intrinsic instability of the oxyme tosylates. Thus, some α-aminoketals **9**[14] and **11** bearing 4-amino phenyl groups were obtained by Pd-catalyzed amination[12] of bromophenyl or reduction of the nitro group followed by acetylation (Scheme 2). Imidate hydrochloride, another key intermediate, was readily obtained from ethyl cyanoacetate by treatment with HCl(g)/EtOH.[13]

The condensation and cyclization reactions were carried out by a one-pot method. As shown in Table 1, the α-aminoketals were treated with imidate hydrochloride in refluxing EtOH for 5 h and then acid solution was added. Heating the resultant mixture under reflux for 12 h yielded the imidazoles. Initially, we attempted the cyclization of amidines **6** in refluxing aqueous 2 N-HCl solution, but the desired imidazole **3a** was obtained in less than 5% yield due to hydrolysis of the ester group

Table 1.



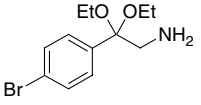
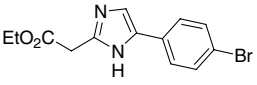
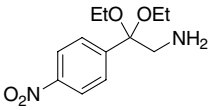
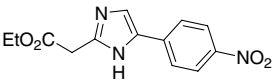
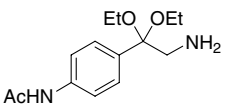
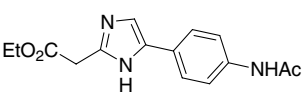
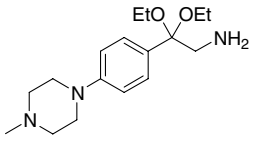
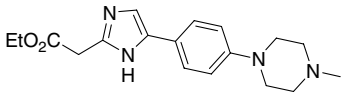
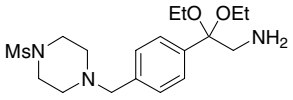
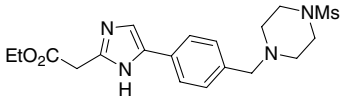
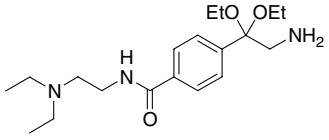
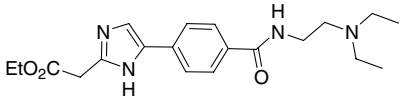
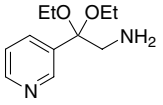
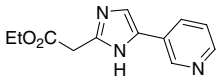
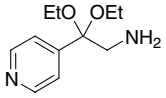
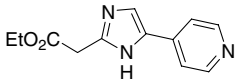
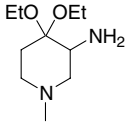
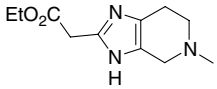
Entry	α-Aminoketals	Products	Yield (%)[a]
1	 **1a**	 **3a**	5[b]
2	**1a**	**3a**	48[c]
3	**1a**	**3a**	61
4	 **1b**	 **3b**	56
5	 **1c**	 **3c**	52

Table 1 (*continued*)

Entry	α-Aminoketals	Products	Yield (%)[a]
6	 **1d**	 **3d**	48
7	 **1e**	 **3e**	35
8	 **1f**	 **3f**	42
9	 **1g**	 **3g**	64
10	 **1h**	 **3h**	0
11	 **1i**	 **3i**	72

[a] All reactions were carried out for 12 h in 25% v/v 4 M-HCl/Dioxane in EtOH unless otherwise stated.
[b] After removal of EtOH, the reaction was carried out in 2 N-HCl aqueous solution.
[c] The reaction was carried out in 25% v/v CF_3COOH in EtOH.

(entry 1). In order to avoid hydrolysis, the cyclization was carried out in non-aqueous acids 4 M-HCl/Dioxane and TFA (entries 2 and 3). Under these reaction conditions, the imidazole **3**[14] was obtained in moderate yields. A better yield and a cleaner reaction was obtained with 4 M-HCl/Dioxane than with TFA. No significant difference was observed for the electron-rich (entries 5 and 6) and electron-deficient (entries 4 and 8) phenyl groups; the rates and yields of the reactions were comparable. *N*-Acyl, *N*-mesyl and amide groups (entries 5–8) are tolerated under these conditions. Those reactions produced moderate yields (35–56%). Similar treatment of α-aminoketals **1g** containing a 3-pyridyl group produced imidazole **3g** in a 64% isolated yield. Interestingly, amidine intermediate of α-aminoketals **1h** containing 4-pyridyl group produced under the same reaction conditions a complex mixture of product and the desired product could not be detected. Both prolonged reaction time and different acid systems resulted in the slow decomposition of amidine. For the formation of the bicyclic ring system (entry 11), the cyclization into 4,5,6,7-tetrahydro-3*H*-imidazo[4,5-*c*]pyridine required shorter reaction times (8 h) and produced slightly higher yields (72%).

In conclusion, we developed a method for the preparation of a variety of substituted 2-imidazol-2-ylacetates, which are pharmacologically useful intermediates. Condensation of α-aminoketals with imidates, followed by cyclization in refluxing 4 M-HCl/Dioxane, provides rapid access to 2-imidazole-2-ylacetates.

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14. Representative spectroscopic data. Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.16 (m, 4H), 3.68 (s, 2H), 3.45–3.38 (m, 4H), 3.12 (t, $J = 5.1$ Hz, 4H), 2.57 (t, $J = 5.1$ Hz, 4H), 2.35 (s, 3H), 1.22–1.15 (m, 6H). Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, $J = 8.5$ Hz, 2H), 7.48 (d, $J = 8.5$ Hz, 2H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.93 (s, 2H), 1.31 (t, $J = 7.2$ Hz, 3H). Compound **3b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (br s, 1H), 8.22 (d, $J = 8.9$ Hz, 2H), 7.90 (d, $J = 8.9$ Hz, 2H), 7.45 (d, $J = 1.8$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 3.96 (s, 1H), 1.33 (t, $J = 7.2$ Hz, 3H). Compound **3d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, $J = 8.8$ Hz, 2H), 7.15 (s, 1H), 6.93 (d, $J = 8.8$ Hz, 2H), 4.23 (q, $J = 7.1$ Hz, 2H), 3.92 (s, 2H), 3.23 (t, $J = 4.6$ Hz, 4H), 2.58 (t, $J = 4.6$ Hz, 4H), 2.35 (s, 3H), 1.31 (t, $J = 7.1$ Hz, 3H). Compound **3g**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (br s, 1H), 8.95 (s, 1H), 8.48–8.46 (m, 1H), 8.04 (m, 1H), 7.35 (s, 1H), 7.32–7.27 (m, 1H), 4.25 (q, $J = 7.2$ Hz, 2H), 3.95 (s, 2H), 1.32 (t, $J = 7.2$ Hz, 3H). Compound **3i**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.19 (q, $J = 7.1$ Hz, 2H), 3.79 (s, 2H), 3.45 (s, 2H), 2.73–2.67 (m, 4H), 2.48 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H).