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A new facile method for the synthesis of 1-arylimidazole-5-carboxylates

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Abstract

A new facile method for the preparation of 1-arylimidazole-5-carboxylates was developed. The new method involved reaction of anilines and ethyl glyoxylate in methanol to give α-anilino-α-methoxyacetates followed by cyclization with TosMIC, affording 1-arylimidazole-5-carboxylates in two steps in 40–94% overall yields.

1-Arylimidazole-5-carboxylic esters are a class of important intermediates in organic synthesis. For example, they were used in the synthesis of biologically active compounds such as fungicides,[1–3] herbicides,[1–3] and plant growth regulators,[1,2,4–6] in the synthesis of analogs of histidine and histamine,[7] and in the synthesis of phenylimidazoles for treatment of cerebral disorders, amnesia, and senile dementia.[8] More recently, 1-arylimidazole-5-carboxylic esters found applications in the synthesis of Factor Xa inhibitors.[9–11]

1-Arylimidazole-5-carboxylic esters were originally prepared via a six-step sequence involving β-hydroxy-α-(*N*-formyl-*N*-aryl)amino acrylates.[12] Reaction of aniline hydrochloride with formalin and potassium cyanide followed by treatment of the resulting anilinoacetonitrile **1** with alcohol in the presence of HCl gave *N*-arylglycine ester **2**. *N*-Formylation of **2** with mixed formic acetic anhydride afforded *N*-formyl-*N*-arylglycine ester **3**. Condensation of **3** with formate and sodium alkoxide gave rise to β-hydroxy-α-(*N*-formyl-*N*-aryl)amino acrylate **4**. Cyclization of **4** with KSCN resulted in formation of 2-mercapto-1-arylimidazole-5-carboxylic ester **5** which, after oxidative desulfurization using nitric acid, gave 1-arylimidazole-5-carboxylic ester **6**. While the overall yields for this method were usually satisfactory, the number of steps involved in the synthesis and the use of potassium cyanide made it unpractical especially for large-scale synthesis. As a consequence, a number of improvements were made to the original synthesis which include

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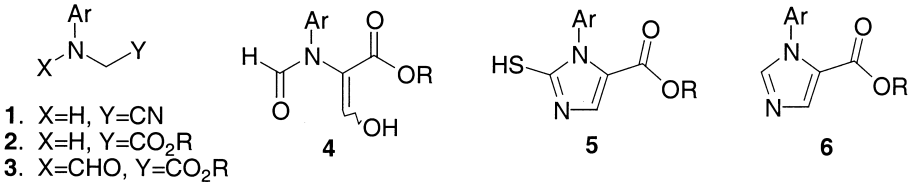
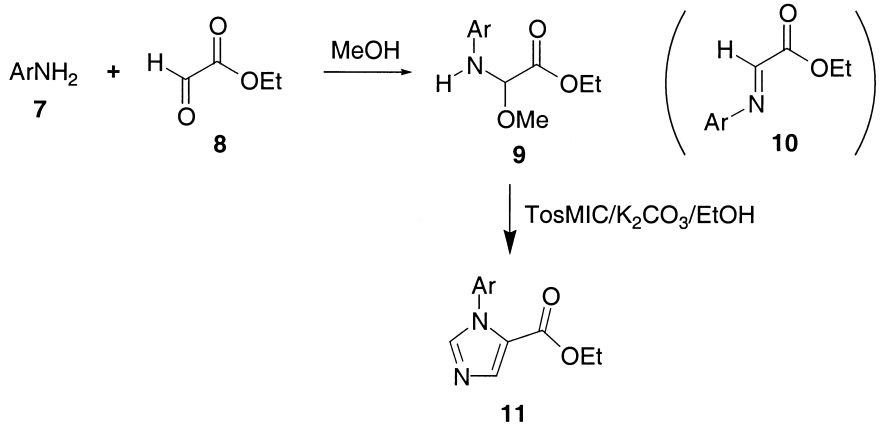
the direct formation of *N*-arylglycine esters **2** from anilines and α-haloacetates,[13] direct preparation of *N*-formyl-*N*-arylglycine esters **3** from *N*-formyl anilines and α-haloacetates,[14] direct preparation of β-hydroxy-α-(*N*-formyl-*N*-phenyl)amino acrylates **4** from *N*-arylglycine esters,[14] and direct imidazole ring formation using formamide at high temperature to eliminate the oxidative desulfurization step.[1–4] In a program of our drug discovery, we required easy access to large amounts of 1-arylimidazole-5-carboxylic esters. Herein, we describe a facile method for the preparation of the title compounds.



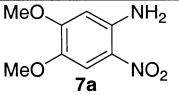
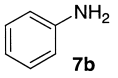
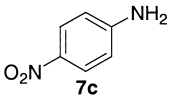
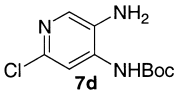
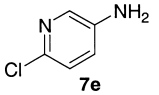
Base-promoted cyclization of *N*-arylimines with (*p*-tolylsulfonyl)methyl isocyanide (TosMIC) is an efficient method for the preparation of 1,5-disubstituted imidazoles.[15] Our initial idea was to prepare imino-glyoxylates from anilines and glyoxylates and subject them to reaction with TosMIC. Thus, treatment of 2-nitro-4,5-dimethoxyaniline **7a** with ethyl glyoxylate **8** in methanol at reflux overnight afforded a crystalline compound after cooling and filtration. It was interesting to note that the desired imino proton was not observed in the proton NMR. Instead, an extra methoxy singlet peak appeared at 3.34 ppm in addition to two sets of doublets at 5.35 and 9.13 ppm corresponding to the α-methine proton and NH proton, respectively. These, in addition to the LC/MS results (M+H = 315), indicated that the resulting product is α-anilino-α-methoxyacetate **9a** rather than the expected imino-glyoxylate **10a**. We envisioned, however, that this α-anilino-α-methoxyacetate **9a** could still be a useful substrate for imidazole ring formation. Under the reaction conditions, **9a** may undergo elimination to give imino-glyoxylate **10a** in situ which would, as expected, react with TosMIC reagent resulting in formation of 1-arylimidazole-5-carboxylate **11a** (Scheme 1).[16] Indeed, treatment of **9a** with TosMIC in refluxing ethanol in the presence of potassium carbonate afforded **11a** in 68% yield.



Scheme 1.

The formation of α-anilino-α-methoxyacetates from anilines and glyoxylates in methanol and subsequent cyclization with TosMIC reagent to yield 1-arylimidazole-5-carboxylates appeared to be general (Table 1). The new method is applicable to electron-rich anilines (Table 1, entry 2) as well as electron-deficient anilines (Table 1, entry 4). In addition, this method also worked with heterocyclic anilines (Table 1, entries 5 and 6).

Table 1
Preparation of α-anilino-α-methoxyacetates **9** and 1-arylimidazole-5-carboxylates **11**[18]

Entry	$ArNH_2$	Conditions 7/8	Time	Yield % (9)[a]	Conditions 9/TosMIC/K_2CO_3	Temp./Time	Yield % (11)[d]
1	 **7a**	1.0/1.0	34h	44%[b]			
2		1.0/5.0	17h	89%	1.0/1.2/2.0	50°C/4h	68%
3	 **7b**	1.0/5.0	18h	--[c]	1.0/1.2/2.0	65°C/4h	40%[e,f,g]
4	 **7c**	1.0/5.0	18h	95%	1.0/1.2/2.0	65°C/3h	89%
5	 **7d**	1.0/1.3	5h	98%	1.0/2.5/4.0	60°C/3h	96%
6	 **7e**	1.0/2.5	18h	--[c]	1.0/2.5/5.0	60°C/8h	48%[f]

[a]Isolated yield unless otherwise indicated. [b]% conversion by HPLC area. [c]Product not isolated. [d]Isolated yield by crystallization unless otherwise indicated. [e]Isolated by flash chromatography. [f]Overall isolated yield for two steps. [g]mp for **11b**: 82-83 °C, Lit.[12] 80-81 °C

In summary, a new facile method for the preparation of 1-arylimidazole-5-carboxylates was developed. The new method involves condensation of anilines and a glyoxylate in methanol to give α-anilino-α-methoxyacetates followed by cyclization with TosMIC, affording 1-arylimidazole-5-carboxylates in two steps in 40–94% overall yields. The application of 1-arylimidazole-5-carboxylates to the synthesis of other biologically active agents will be reported in due course.

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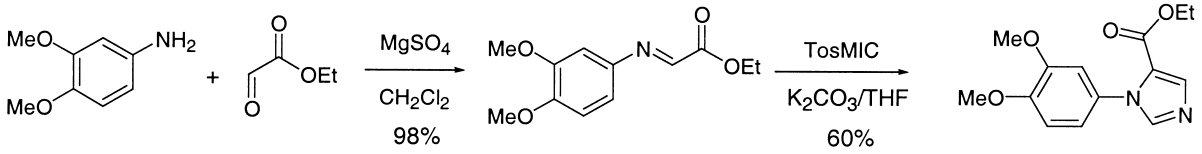
16. In a separate experiment, 4-aminoveratrole was condensed with ethyl glyoxylate following literature conditions[17] to give the corresponding imino-glyoxylate which upon treatment with TOSMIC/K_2CO_3 in THF gave 1-(3,4-dimethoxyphenyl)imidazole-5-carboxylic ethyl ester.



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18. ^{1}H NMR spectroscopic data for: compound **11a** ($CDCl_3$) δ 7.87 (s, 1H), 7.78 (s, 1H), 7.67 (s, 1H), 6.80 (s, 1H), 4.18 (q, J = 7.1 Hz, 2H), 4.03 (s, 3H), 3.97 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); compound **11b** (DMSO-d_6) δ 8.10 (s, 1H), 7.80 (s, 1H), 7.42–7.52 (m, 5H), 4.12 (q, J = 7.1 Hz, 2H), 1.14 (t, J = 7.1 Hz, 3H); compound **11c** (DMSO-d_6) δ 8.35 (d, J = 8.7 Hz, 2H), 8.24 (s, 1H), 7.86 (s, 1H), 7.79 (d, J = 8.7 Hz, 2H), 4.16 (q, J = 7.1 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H); compound **11d** ($CDCl_3$) δ 8.35 (s, 1H), 8.07 (s, 1H), 7.98 (s, 1H), 7.65 (s, 1H), 6.22 (br s, 1H), 4.24 (q, J = 7.1 Hz, 2H), 1.49 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H); compound **11e** ($CDCl_3$) δ 8.41 (S, 1H), 7.90 (s, 1H), 7.70 (d, J = 8.6 Hz, 1H), 7.69 (s, 1H), 7.48 (d, J = 9.6 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).