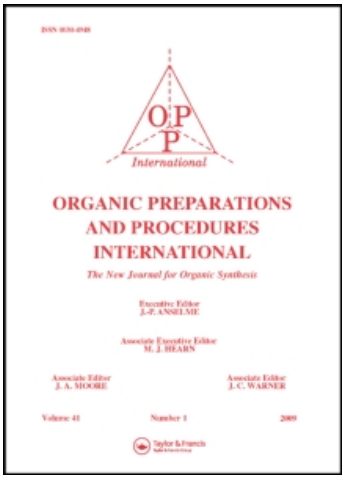

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EFFICIENT SYNTHESIS OF IMIDAZO[2,1-*a*]ISOQUINOLINES USING A HYPERVALENT IODINE(III) SULFONATE

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(07/27/04)

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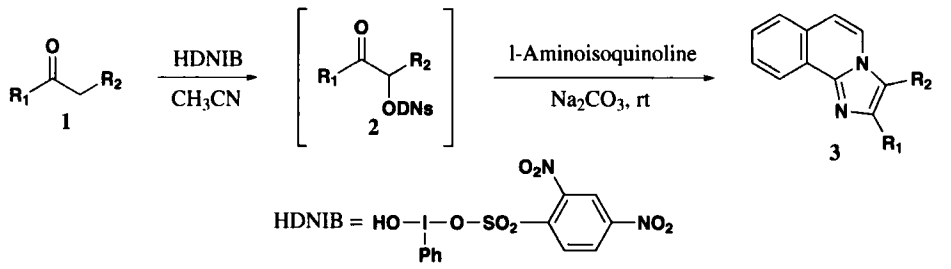
Imidazo[2,1-*a*]isoquinolines are of interest due to their antiinflammatory,[1] potential antirhinoviral,[2] long-acting local anesthetic[3] and antiulcer properties.[4] They also have been shown to have biological activity as non-hormonal contragestational agents in both hamsters and rats.[5] The methods used for their synthesis involve the cyclization of phenacylisoquinolinium bromide with ammonium acetate in acetic acid,[6] reaction of α-bromoacetophenone phenylsulfonylhydrazones with isoquinoline,[7] 1,5-dipolar cyclization reaction of isoquinolinium *N*-ylides using *N-bis*(methylthio)methylene-*p*-toluenesulfonamide[8] and condensation of 1-amino-2-(α-benzotriazol-1-ylmethyl) isoquinolinium chloride with aryl aldehydes.[9]

Recently, hypervalent iodine(III) reagents have been used extensively in organic synthesis due to their low toxicity, ready availability and easy handling.[10] As a continuation of our studies concerning hypervalent iodine(III) chemistry, we have reported a modified Pictet-Spengler cyclization of *N*-sulfonyl-β-phenethylamines with ethyl methylthioacetate using *bis*(trifluoroacetoxyiodo)benzene (BTI) to prepare ethyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylates.[11] We report here a new and direct method for the synthesis of imidazo[2,1-*a*]isoquinoline (**3**) by the cyclocondensation of 1-aminoisoquinoline with α-[2,4-(dinitrobenzene)sulfonyloxy carbonyl compounds (**2**), formed *in situ* from the reaction of [hydroxy-(2,4-dinitrobenzenesulfonyloxy)iodo] benzene (HDNIB) with aryl methyl ketones (**1**). The required HDNIB was prepared in satisfactory yields from the reaction of 2,4-dinitrobenzenesulfonic acid with phenyliodine(III) diacetate (PIDA). Treatment of aromatic ketones with HDNIB in CH_3CN at reflux for 1 h produced the α-[(2,4-dinitrobenzene)sulfonyl]oxy ketone intermediates (**2**). Subsequent cyclocondensation by 1-aminoisoquinoline at room temperature in the presence of sodium carbonate gave the corresponding imidazo[2,1-*a*]isoquinoline derivatives (**3**) in good yields as shown in the Scheme.

The 2,4-dinitrobenzenesulfonyloxy group located at the α position to a carbonyl group represents an increasingly important entity in both mechanistic and synthetic organic chemistry. One reason for this importance is that the 2,4-dinitrobenzenesulfonyloxy group is a good leaving group, and this accounts for the considerable synthetic utility associated with these groups in functionalization of carbonyl compounds.



DNs = 2,4-dinitrobenzenesulfonyl

a) $R_1 = C_6H_5$, R_2 = H; b) R_1 = 4-MeC_6H_4, R_2 = H; c) R_1 = 4-$MeOC_6H_4$, R_2 = H; d) R_1 = 4-FC_6H_4, R_2 = H; e) R_1 = 4-ClC_6H_4, R_2 = H; f) R_1 = 4-BrC_6H_4, R_2 = H; g) R_1 = 3,4-$Cl_2C_6H_3$, R_2 = H; h) R_1 = 3-Furyl, R_2 = H; i) R_1 = 3-Thienyl, R_2 = H; j) $R_1 = C_6H_5$, R_2 = Me

Our experiments involving a one-pot procedure for the preparation of imidazo[2,1-*a*]isoquinoline derivatives (**3**) by cyclocondensation of ketones with HDNIB and 1-aminoisoquinoline at room temperature in CH_3CN were successful. The results are summarized in the Table. When the reaction was conducted by replacing HDNIB with HTIB (Koser's reagent)[12] under the same conditions, the preparation of 2-phenylimidazo[2,1-*a*]isoquinoline (**3a**) requires refluxing for 6 h. This observation clearly demonstrated that the leaving ability of –ODNs is superior to –OTs in nucleophilic substitution reactions.

Table. Preparation of Imidazo[2,1-*a*]isoquinolines **3a-j**

Cmpd[a]	Yield (%)	mp (°C)	*lit.* mp (°C)
3a	80	141-142	140-141[13]
3b	73	159-160	157-158[13]
3c	82	177-179	176-178[13]
3d	80	162-163	163-164[13]
3e	72	189-191	188-190[13]
3f	71	199-200	197-198[13]
3g	75	161-162	160-162[13]
3h	82	105-106	106-107[14]
3i	80	122-124	123-125[14]
3j	76	175-176	177-178[15]

a) All products are known compounds and their physical constants, IR and ^{1}H NMR spectra correspond to those reported in the literature.

In summary, the method described herein provides a good approach for the synthesis of imidazo[2,1-*a*]isoquinolines by the reaction of aryl methyl ketones with hypervalent iodine(III) sulfonate (HDNIB) in a one-pot procedure and gives good yields.

Typical Procedure.- A mixture of acetophenone (120 mg, 1.0 mmol) and HDNIB (468 mg, 1.0 mmol) in acetonitrile (20 mL) was heated at reflux for 1 h. After the reaction mixture had been cooled to room temperature, 1-aminoisoquinoline (172.8 mg, 1.2 mmol) and Na_2CO_3 (106 mg, 1.0 mmol) were added and the mixture was stirred at room temperature for 1 h. Subsequently, the solvent was evaporated off and the residue was purified by chromatography on a silica gel column eluting with AcOEt-cyclohexane (1:2) to give **3a** in 80% yield. The identity of the purified compounds was confirmed by comparison with authentic samples.

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A CLEAN AND RAPID SYNTHESIS OF 5-AMINO AND 5-ALKOXYCARBONYLPYRAZOLES USING MONTOMORILLONITE UNDER ACID FREE CONDITIONS

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5-Aminopyrazoles are compounds of considerable medicinal interest as they exhibit antiinflammatory and antipyretic properties.[1] These derivatives are also useful intermediates in the synthesis of several fused pyrazoles of potential biological interest.[2, 3] 5-Alkoxycarbonyl pyrazoles are also important intermediates in the synthesis of agrochemicals, microbiocides, plant growth regulators[4] and anticoagulant factor Xa inhibitors.[5] The most common method of synthesizing 5-aminopyrazoles involves the condensation of β-ketonitriles (**2**) with hydrazines (**1**) under a variety of conditions. These include refluxing **2** with **1** in ethanol for 8-16 hrs and reaction of **1** with **2** in presence of large excess of hydrochloric acid.[6] Cyclization of **2** with **1** in refluxing ethanol in presence of triethylamine[7] and 10% acetic acid have also been reported.[8] However, all these methods suffer from certain disadvantages like long reaction times,[9] strongly acidic[6] or basic conditions.[7]