

An Optimized Process for Formation of 2,4-Disubstituted Imidazoles from Condensation of Amidines and α -Haloketones

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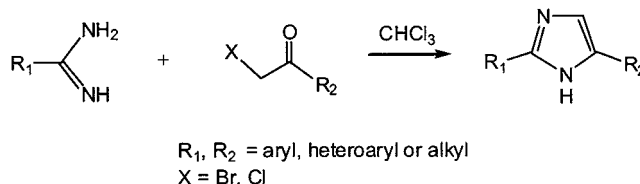
Abstract:

The preparation of 2,4-disubstituted imidazoles from the condensation of α -haloketones with amidines is described. The optimal reaction protocol is to add the α -bromoketone solution to the amidine in aqueous tetrahydrofuran in the presence of potassium bicarbonate under vigorous reflux. Imidazole was isolated in 83–91% yield with >95% purity without column chromatography.

Introduction

The imidazole nucleus is often found in biologically active molecules,¹ and a large variety of methods have been employed for their synthesis.² We recently had a need to develop a more viable process for the preparation of multikilogram quantities of 2,4-disubstituted imidazoles. The condensation of amidines, which are readily accessible from nitriles,³ with α -haloketones has become a widely used method for the synthesis of 2,4-disubstituted imidazoles (Scheme 1). A literature survey showed that chloroform was the most commonly used solvent for this reaction.⁴ In addition to the use of a nonbenign solvent, yields of the reaction varied from poor to moderate, and column chromatography was often needed for product isolation. Use of other solvents such as alcohols,⁵ DMF,⁶ and acetonitrile⁷ have also been reported for this reaction, but yields are also frequently poor.

Scheme 1



Results and Discussion

Our initial attempts to optimize this reaction focused on utilizing anhydrous reaction conditions due to stability concerns of α -bromoketones under basic aqueous conditions. Condensations using a variety of bases (potassium *tert*-butoxide, potassium carbonate, cesium carbonate, etc.) in THF, DMF, CH_3CN , or CH_2Cl_2 gave low yields. Reactions in alcohols (ethanol, 2-propanol, and *tert*-butyl alcohol) were also unsatisfactory. We then investigated mixed organic/aqueous reaction media, as we reasoned that amidines are stronger nucleophiles than water, and therefore the condensation rate of α -bromoketones with amidines should be faster than the decomposition rate of the bromoketone in water. A series of reactions using THF, DMF, or alcohols as the organic solvent were conducted, and from these experiments we made a number of observations.

(1) Aqueous THF is a suitable media to bring the very polar amidines and nonpolar α -bromoketones in the same phase, and it is superior to aqueous DMF or alcohol.

(2) Higher reaction temperatures in aqueous THF accelerates the condensation.

(3) Bicarbonate is the base of choice, as it only serves to scavenge the acid produced during the condensation reaction.

(4) As α -bromoketones decompose under the reaction conditions, their concentrations in the reaction should be minimized.

We found that the optimal reaction protocol was to add a solution of α -bromoketone in THF to the amidine in aqueous THF in the presence of potassium bicarbonate under vigorous reflux. Once the reaction was complete, the THF was removed, and the product crystallized directly out of the remaining solvent. Using this protocol, 2,4-disubstituted

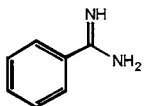
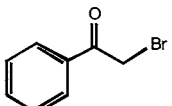
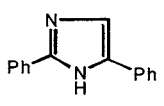
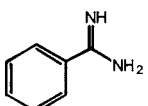
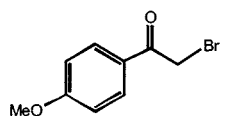
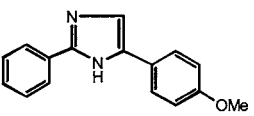
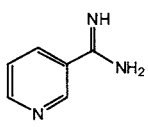
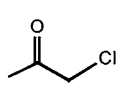
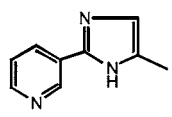
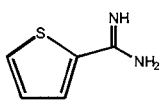
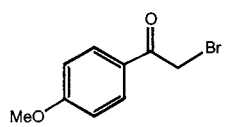
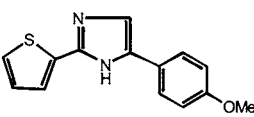
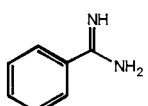
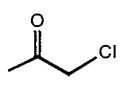
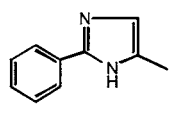
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Table 1. Amidine and α -haloketone condensations

Amidine	α -haloketone	Product	Isolated Yields	Lit. Yields
			86%	62% ^{a 8}
			91%	50% ⁹
			83%	15% ¹⁰
			87%	80% ^{b 11}
			87%	59% ^{c 12}

^a It was reported that the results were irreproducible. ^b 3 equiv of 2-thiophenylamidinium was used, yield was based on α -bromoketone. ^c From condensation of amidine and α -haloketone.

imidazoles were isolated in excellent yields with >95% purity without column chromatography. Aromatic and aliphatic α -haloketones participate in this reaction with a variety of aromatic amidines, as indicated in Table 1. We note that reactions involving pyridylamidines or chloroacetone are substantially more robust using this protocol (entries 3 and 4). We have successfully used this protocol on multikilogram scale.

In conclusion, a scaleable process for the preparation of 2,4-substituted imidazole from amidines and α -haloketones has been described. This method avoids the use of chloroform as solvent and affords the desired products in consistently good-to-excellent yields.

Experimental Section

HPLC analyses were carried out using a Zorbax SB-CN column (4.6 mm \times 250 mm), eluting with acetonitrile/water (30/70, 2 mL/min) monitored at 210 nm wavelength. A Finnigan (San Jose, CA) LCQ ion trap instrument coupled to an HP 1100 liquid chromatograph was used for all MS data acquisition. NMR spectra were recorded in DMSO- d_6 with DMSO- d_6 (^1H , 2.49 ppm, ^{13}C , 39.5 ppm) as an internal reference, using Varian 400. 2,4-Disubstituted imidazoles in Table 1 were previously characterized in the literature.

Spectroscopic data of all products were consistent to those reported.

Typical Procedure. A mixture of 3-amidinopyridine hydrochloride (150 g, 0.95 mol) and potassium bicarbonate (381 g, 3.80 mol) in 1.6 L of THF and 400 mL of water was heated at vigorous reflux. Chloroacetone (80 mL, 0.95 mol) in THF (400 mL) was added over a period of 30 min, while keeping the reaction mixture at reflux. After the addition, the reaction was heated at reflux for 2 h until HPLC assay showed reaction completion. THF was then removed by distillation, and the solids that crystallized out were collected by filtration and rinsed once with water. The crude product (94.3% pure by HPLC) was repurified in isopropyl ether/hexanes (1:1 mixture, 600 mL) for 2 h, filtered, and dried under vacuum to give 126.4 g (82.7% yield, 99.1% pure by HPLC) of the desired product as an off-white solid.

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