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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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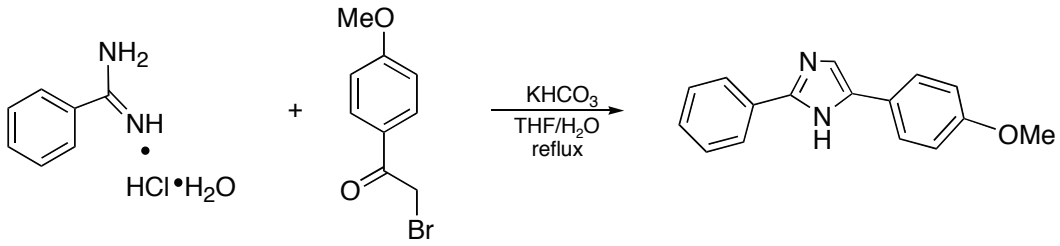
PREPARATION OF 2,4-DISUBSTITUTED IMIDAZOLES: 4-(4-METHOXYPHENYL)-2-PHENYL-1H-IMIDAZOLE [1H-Imidazole, 4-(4-methoxyphenyl)-2-phenyl-]



Submitted by Bryan Li,[1] Charles K-F Chiu, Richard F. Hank, Jerry Murry, Joshua Roth, and Harry Tobiassen.
Checked by Renee Kontnik and Steven Wolff.

1. Procedure

4-(4-Methoxyphenyl)-2-phenyl-1H-imidazole. A 2-L, three-necked, round-bottomed flask equipped with an addition funnel, reflux condenser, and mechanical stirrer is charged with 500 mL of tetrahydrofuran (THF) and 125 mL of water. Benzamidine hydrochloride monohydrate (50 g, 0.29 mol) (Note 1) is added, followed by the slow, portionwise addition of potassium bicarbonate (54.4 g, 0.57 mol) (Note 2). The reaction mixture is vigorously heated to reflux. A solution of 4-methoxyphenacyl bromide (65.3 g, 0.29 mol) in 325 mL of THF is then added dropwise via the addition funnel over a period of 30 min while the reaction is maintained at reflux. After completion of the addition, the mixture is heated at reflux for 18-20 hr (Note 3), then cooled in an ice bath (Note 4), and THF is removed under reduced pressure using a rotary evaporator. An additional 100 mL of water is added, and the resulting suspension is stirred at 50-60 °C for 30 min. The mixture is cooled in an ice bath and the solids are collected by filtration. The filter cake is rinsed with two 100-mL portions of water and air-dried in the filter funnel for 2 h. The crude product is transferred to a 500-mL flask and 150 mL of diisopropyl ether and 150 mL of hexanes are added. The mixture is stirred for 2 h at room temperature, and the solids are again collected by filtration. The filter cake is dried in a vacuum oven for 48 h (68 °C/ca. 100 mm) to give 68.6 g (96%) of the desired imidazole as an off-white solid (Notes 5, 6).

2. Notes

1. All reagents were purchased from Aldrich Chemical Company and used without further purification.

2. Caution: liberation of carbon dioxide.

3. TLC analysis (elution with 1:1 hexanes:ethyl acetate) indicated that the reaction was not complete after 5 h; heating was continued overnight.

4. Inorganic salts are observed upon cooling and are removed by decantation.

5. The dried product contained 0.10-0.54% H_2O w/w; and has the following physical properties: mp 144.5-145.6 °C [lit. mp 178-179 °C[2]]; IR (KBr): cm^{-1} 3003, 2836, 1617, 1567, 1499, 1461, 1403, 1298, 1248, 1176; ^1H NMR (300 MHz, DMSO-d^6): δ 3.76 (s, 3H), 6.94 (d, J = 8.4 Hz, 2H), 7.46-7.30 (m, 3H), 7.58 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H), δ 7.97 (d, J = 7.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d^6): δ 55.0, 114.0, 115.8, 124.9, 125.7, 126.4, 127.9, 128.6, 130.7, 139.2, 145.8, 158.1. MS *m/z* 250 ($[M]^+$); 235 ($[M-CH_3]$); 77 ($[C_6H_6]$); Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found C, 76.49; H, 5.62; N, 11.03.

6. HPLC analysis indicated 97.1 area % purity. HPLC conditions: Zorbax XDB-C8 column (3.0 x 100mm) eluting with 5-100% MeCN + 0.1%TFA (0.5 mL/min); 220 nm wavelength.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practice in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The imidazole nucleus is often found in biologically active molecules,[3] and a large variety of methods have been employed for their synthesis.[4] We recently needed to develop a more viable process for the preparation of kilogram quantities of 2,4-disubstituted imidazoles. The

condensation of amidines, which are readily accessible from nitriles,[5] with α-halo ketones has become a widely used method for the synthesis of 2,4-disubstituted imidazoles. A literature survey indicated that chloroform was the most commonly used solvent for this reaction.[6] In addition to the use of a toxic solvent, yields of the reaction varied from poor to moderate, and column chromatography was often required for product isolation. Use of other solvents such as alcohols,[7] DMF,[8] and acetonitrile[9] have also been utilized in this reaction, but yields are also frequently been reported as poor.

Our initial attempts to optimize this reaction focused on utilizing anhydrous reaction conditions due to stability concerns of α-bromo ketones under basic aqueous conditions. Condensations using a variety of bases (potassium *t*-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 *t*-butyl alcohol) were equally unsatisfactory. We then investigated mixed organic/aqueous reaction media, since we reasoned that amidines are stronger nucleophiles than water, and therefore the condensation rate of α-bromo ketones with amidines should be faster than the decomposition rate of the bromo ketones in water. A series of reactions using THF, DMF and alcohols as the organic solvent were conducted, and from these experiments we made a number of observations.

(1) Aqueous THF is a suitable solvent system to solubilize the very polar amidines and non-polar α-bromo ketones, and it is superior to aqueous DMF or alcohol.
(2) Higher reaction temperatures in aqueous THF accelerate the condensation.
(3) Bicarbonate is the base of choice, since it only scavenges the acid produced during the condensation reaction.
(4) Since α-bromo ketones decompose under the reaction conditions, their concentration in the reaction should be minimized.

We found that the optimal reaction protocol was to add a solution of α-bromo ketone in THF to the amidine in aqueous THF in the presence of potassium bicarbonate under vigorous reflux. Using this procedure, 2,4-disubstituted imidazoles were isolated in excellent yields with >95% purity without column chromatography. Aromatic and aliphatic α-halo ketones participate in this reaction with a variety of aromatic amidines, as indicated in Table 1. Particularly noteworthy is that reactions involving

pyridylamidines or chloroacetone are substantially more robust using this process (entries 3 and 4). We have successfully used this protocol on a multi-kilogram scale.

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

Table 1. Amidine and α-Halo ketone Condensations[a]

Amidine	α-Halo ketone	Product	Isolated Yields	Lit. Yields
Benzamidine	2-Bromo-acetophenone	2,5-Diphenyl-1*H*-imidazole	86%	62% [b 10]
Nicotinamidine	Chloroacetone	3-(5-Methyl-1*H*-imidazol-2-yl)-pyridine	83%	15% [11]
Thiophene-2-carboxamidine	2-Bromo-4'-methoxy-acetophenone	5-(4-Methoxyphenyl)-2-thiophen-2-yl-1*H*-imidazole	87%	80%[c 12]
Benzamidine	Chloroacetone	5-Methyl-2-phenyl-1*H*-imidazole	87%	59%[d 13]

[a] The 2,4-disubstituted imidazoles in Table 1 were previously characterized in the literature. The spectroscopic data of all products are consistent to that originally reported.

[b] Irreproducible results were reported.

[c] 3 eq. of 2-thiophenylamidine was used; yield was based on the α-bromo ketone.

[d] From the condensation of amidine and an α-halo oxime.

1. Chemical Research and Development, Pfizer Global Research and Development, Groton Laboratories, Groton, CT 06340, USA. Jerry Murry is currently located at Process Research Department, Merck Research Laboratories, Merck and Co. Inc., Rahway, NJ, 07065.

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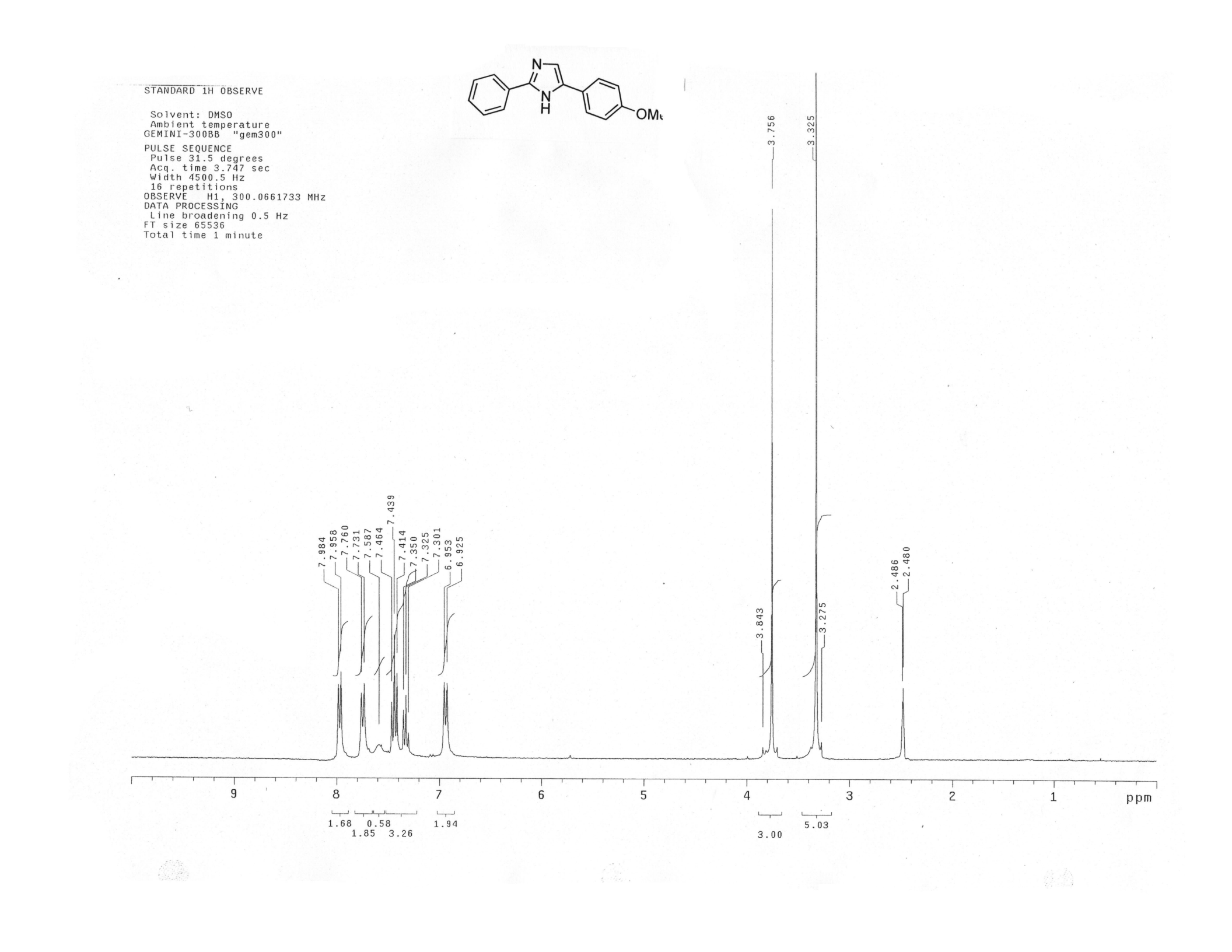
Appendix
Chemical Abstracts Nomenclature (Registry Number)

4-(4-Methoxyphenyl)-2-phenyl-1H-imidazole: 1H-Imidazole, 4-(methoxyphenyl)- 2-phenyl-; (53458-08-5)

Benzamidine hydrochloride: Benzenecarboximidamide, monohydrochloride; (1670-14-0)

4-Methoxyphenacyl bromide; Ethanone, 2-bromo-1-(4-methoxyphenyl)-; (2632-13-5)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Acq. time 3.747 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0661733 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 minute
N
H
OM
7.984
7.958
7.760
7.731
7.587
7.464
7.439
7.414
7.350
7.325
7.301
6.953
6.925
3.843
3.756
3.325
3.275
2.486
2.480
9
8
7
6
5
4
3
2
1
ppm
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1.85
3.26
1.94
3.00
5.03