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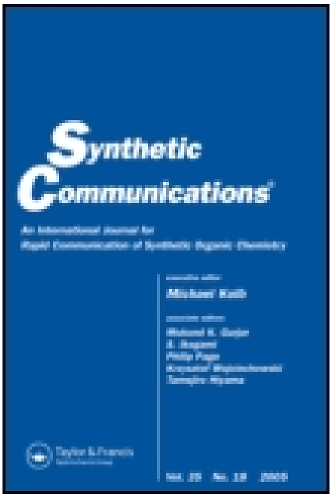

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Research on the Synthesis of Aromatic Hydrazone in Ionic Liquids

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RESEARCH ON THE SYNTHESIS OF AROMATIC HYDRAZONE IN IONIC LIQUIDS

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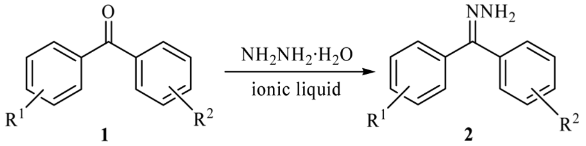
GRAPHICAL ABSTRACT



a, $R^1 = H$, $R^2 = H$; b, $R^1 = 4\text{-Cl}$, $R^2 = NO_2$; c, $R^1 = 4\text{-Br}$, $R^2 = NO_2$; d, $R^1 = 4\text{-CH(CH}_3)_2$, $R^2 = NO_2$; e, $R^1 = 4\text{-Cl}$, $R^2 = 4\text{-NO}_2$; f, $R^1 = 4\text{-Cl}$, $R^2 = 4\text{-NH}_2$; g, $R^1 = 4\text{-Br}$, $R^2 = 4\text{-NH}_2$

Abstract *Aromatic hydrazones are important intermediates for pesticides cibenzoline and cefxime. The methodology of synthesis of aromatic hydrazone from aromatic ketone and hydrazine hydrate in ionic liquid, was described and various aromatic hydrazones were prepared by the reaction of aromatic ketone with hydrazine hydrate in ionic 1iquid at 100 °C with good yields. The ionic liquids could be recycled and reused after the reaction. The influences of the various ionic liquids on the reaction are discussed. The product structure was characterized by infrared, mass spectrometry, NMR spectra, and elemental analysis.*

Keywords Aromatic hydrazone; ionic liquids; synthesis

INTRODUCTION

Aromatic hydrazone derivatives have been claimed to possess interesting bioactivity such as antibacterial, antifungal, anticonvulsant, antimalarial, analgesic, and anticancer activities.[1,2] The mechanism of DNA cleavage by this type of compound is of biochemical and pharmaceutical interest.[3] Therefore, the study of aromatic hydrazone derivatives has important applications.

Our recent interest has been in the area of clean synthesis using ionic liquids as a green recyclable alternative to classical molecular solvents.[4,5] As a part of program to investigate the range of organic reaction possible in ionic liquids, to the best of our knowledge, since 1944 there has been a series of studies on the synthesis of aromatic hydrazone,[6] but no report describing the process for preparing aromatic

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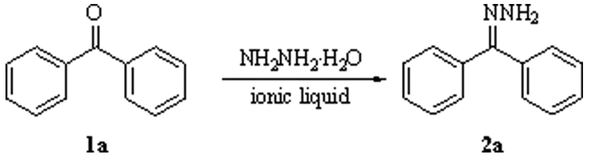
hydrazone derivatives using ionic liquids as reaction media. Therefore, we employed various aromatic ketones as our starting materials to investigate the synthesis of aromatic hydrazone derivatives in ionic liquid media and discuss the influences of the various solvents on the reactions.

RESULTS AND DISCUSSION

First, benzophenone **2a** ($R^1 = H$, $R^2 = H$) was used as model substrate to react with hydrazine hydrate in various solvents (Scheme 1, Table 1). The reaction results demonstrated that ionic liquids do work very well and gave the desired product **2a** in a good yield of 95.2% when **1a** was treated with 3 equiv. of hydrazine hydrate in [Bmim]BF_4 at 100 °C (entry 1). We also found that the reaction proceeded better in ionic liquid [Bmim]BF_4 than [Bmim]PF_6 (entry 2) or [Bmim]CH_3COO (entry 3). Furthermore, we investigated this reaction used recycled ionic liquid five times and found the same result was obtained (entry 4).

Next, a series of aromatic ketone **1** reacted with hydrazine hydrate to give aromatic hydrazones **2**, new compounds, in the one-pot synthesis at 100 °C in [Bmim]BF_4 according to this experimental procedure (Scheme 2, Table 2). In addition,

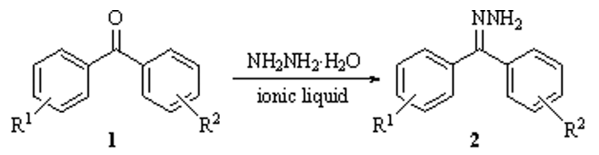


Scheme 1.

Table 1. Synthesis of hydrazone **2a** in various solvents

Entry	Solvent	Yields (%)[a]
1	[Bmim]BF_4	95.2
2	[Bmim]PF_6	93.4
3	[Bmim]CH_3COO	91.2
4[b]	[Bmim]BF_4	95

[a] Isolated yields.
[b] Used recycled ionic liquid.



a, $R^1 = H$, $R^2 = H$; b, $R^1 = 4\text{-}Cl$, $R^2 = NO_2$; c, $R^1 = 4\text{-}Br$, $R^2 = NO_2$; d, $R^1 = 4\text{-}CH(CH_3)_2$, $R^2 = NO_2$; e, $R^1 = 4\text{-}Cl$, $R^2 = 4\text{-}NO_2$; f, $R^1 = 4\text{-}Cl$, $R^2 = 4\text{-}NH_2$; g, $R^1 = 4\text{-}Br$, $R^2 = 4\text{-}NH_2$

Scheme 2.

Table 2. Reactions of different substrates[a]

Compound	R_1	R_2	Yields (%)[b]
2a	4-H	4-H	95.2
2b	4-Cl	4-NO_2	92.9
2c	4-Br	4-NO_2	90.0
2d	4-$CH(CH_3)_2$	4-NO_2	88.8
2e	2,4-Cl_2	4-NO_2	83.7
2f	4-Cl	4-NH_2	81.5
2g	4-Br	4-NH_2	79.3

[a] All reactions were in ionic liquid $[Bmim]BF_4$.

[b] Isolated yields.

we found that better results were obtained used aromatic hydrazone with electron-withdrawing groups **2b**, **2c**, **2d**, and **2e** than with electron-donating groups **2f** and **2g**.

In conclusion, we have successfully developed a green synthetic procedure for preparing aromatic hydrazone derivatives in ionic liquid as reaction media. It is possible to apply this green synthetic method to industrialization.

EXPERIMENTAL

Melting points were uncorrected. ^1H NMR spectra were obtained on a Bruker AC 400 (400-MHz) instrument in $CDCl_3$ using tetramethylsilane (TMS) as internal standard. Infrared (IR) spectra were taken with a Bruker Victor 22 spectrometer. Mass spectra were obtained on a HP 5989B mass spectrometer. Ionic liquids and aromatic ketone were prepared according to the literature method.[7,8]

General Procedure

A three-necked, round-bottomed flask containing a stirring bar was charged with aromatic ketones (1.0 mmol), hydrazine hydrate (2.0 mmol), and ionic liquid (5 mL) at 100 °C using thin-layer chromatography (TLC) to monitor the reaction for about 4 h. After being cooled, the mixture was extracted with $CH_2Cl_2(3 \times 20\,mL)$) or toluene (3×20 mL), and then the organic layers were combined, washed with water, dried with $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography on silica gel using ethyl acetate and hexane (10/90 to 30/70) as eluant. The structure of the compound was confirmed by ^1H NMR, MS, and elemental analysis. The physical and spectra data of the compounds are as follows.

Benzophenone Hydrazone 2a [5350-57-2]

Mp 97–98 °C; MS (70 eV) m/z (%): 196 (M^+, 100), 180 (21).

4-Chloro-4′-nitrobenzophenone Hydrazone 2b

Mp 116–118 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ: 8.14 (d, $J = 8$ Hz, 2H), 7.51–7.60 (m, 4H), 7.23–7.32 (m, 2H), 5.72 (s, 2H); IR (KBr, cm^{-1}): 3432, 3388, 3289, 1633, 1594, 1562, 1513, 1342, 1090, 857, 829, 757, 696; MS (70 eV) *m*/*z* (%): 275 (M^+, 100), 228 (23), 163 (16). Anal. calcd. for $C_{13}H_{10}ClN_3O_2$: C, 56.73; H, 3.64. Found: C, 56.7; H, 3.66.

4-Bromo-4′-nitrobenzophenone Hydrazone 2c

Mp 72–73 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.11–8.15 (m, 2H), 7.76–7.79 (m, 2H), 7.46–7.56 (m, 2H), 7.20–7.24 (m, 2H), 7.06 (s, 2H); IR (KBr, cm^{-1}): 3425, 3289, 1589, 1555, 1503, 1337, 1070, 854, 824, 757, 698; MS (70 eV) *m*/*z* (%): 320 (M^+, 100), 193(24), 177 (25), 163 (54). Anal. calcd. for $C_{13}H_{10}BrN_3O_2$: C, 48.75; H, 3.13. Found: C, 48.77; H, 3.16.

4-Isopropyl-4′-nitrobenzophenone Hydrazone 2d

Mp 116–118 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.37 (d, $J = 8$ Hz, 2H), 8.14 (d, $J = 8$ Hz, 2H), 7.46–7.53 (m, 2H), 7.19 (d, $J = 28$ Hz, 2H), 6.87 (s, 2H), 2.95–3.01 (m, 1H), 1.22 (d, $J = 7.6$ Hz, 6H); IR (KBr, cm^{-1}): 3446, 3300, 2962, 1598, 1555, 1514, 1407, 1384, 1337, 1048, 946, 836; MS (70 eV) *m*/*z* (%): 283 (M^+, 100), 268 (95). Anal. calcd. for $C_{16}H_{17}N_3O_2$: C, 67.84; H, 6.01. Found: C, 67.87; H, 6.03.

2,4-Dichloro-4′-nitrobenzophenone Hydrazone 2e

Mp 172–174 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.15 (d, $J = 9.2$ Hz, 2H), 7.64 (d, $J = 1.6$ Hz, 1H), 7.56 (d, $J = 9.2$ Hz, 2H), 7.48 (d, $J = 9.2$ Hz, 1H), 7.21–7.19 (d, $J = 8$ Hz, 1H), 5.74 (s, 2 H); MS (70 eV) *m*/*z* (%): 309 (M^+, 100). Anal. calcd. for $C_{13}H_9Cl_2N_3O_2$: C, 50.49; H, 2.91. Found: C, 50.47; H, 2.93.

4-Chloro-4′-aminobenzophenone Hydrazone 2f

Mp 125–127 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.59–7.50 (m, 8H), 5.48 (s, 2H), 3.87 (s, 2H); IR (KBr, cm^{-1}): 3424, 3332, 1621, 1512, 1487, 1384, 1329, 1278, 1164, 1090, 1012, 956, 832; MS (70 eV) *m*/*z* (%): 245 (M^+, 100). Anal. calcd. for $C_{13}H_{12}ClN_3$: C, 63.67; H, 4.90. Found: C, 63.69; H, 4.93.

4-Bromo-4′-aminobenzophenone Hydrazone 2g

Mp 89–91 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 6.58–7.66 (m, 8H), 5.49 (s, 2H), 3.86 (s, 2H); IR (KBr, cm^{-1}): 3456, 3424, 3335, 1623, 1513, 1483, 1384, 1338, 1279, 1164, 1070, 1008, 956, 831; MS (70 eV) *m*/*z* (%): 290 (M^+, 100), 273 (10), 199 (20), 93 (48). Anal. calcd. for $C_{13}H_{12}BrN_3$: C, 53.79; H, 4.14. Found: C, 53.78; H, 4.13.

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