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An Efficient One-Pot Procedure for the Preparation of 1,3,4-Thiadiazoles in Ionic Liquid [Bmim]BF_4 as Dual Solvent and Catalyst

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ABSTRACT: *The one-pot three component condensation of hydrazine hydrate with substituted phenylisothiocyanates followed by the addition of substituted benzaldehydes in the presence of ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) and in the absence of any other catalyst under mild condition afforded 1,3,4-thiadiazoles in excellent yields. The reaction workup is simple, and the ionic liquid was easily recovered from the reaction and reused.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:320–324, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20432

INTRODUCTION

1,3,4-Thiadiazoles and related compounds have attracted significant interest in medicinal chemistry and many fields of technology. Some of the technological applications involve dyes [1], lubricating compositions [2], optically active liquid crystals [3], and photographic materials [4]. In the medicinal field, one of the best-known drugs based on 1,3,4-thiadiazole is acetazolamide (Acetazola) [5], which is a carbonic anhydrase inhibitor launched in 1954. In addition, its indications and usage include in glaucoma, epilepsy, and congestive cardiac failure. Thiadiazole derivatives are also found to have antitumor [6a], hypoglycemic [6b], anticonvulsant [6c], hypotensive [6d], antiproliferative [6e], and antituberculotic [6f] activities. As a result of these useful applications, chemists have been encouraged to design new synthetic (both solution and solid phase) methodologies for the preparation of this medicinally important heterocyclic building block.

Literature survey of synthetic methods for these interesting compounds indicates that there are three main categories for the synthesis of 1,3,4-thiadiazoles: (1) cyclizations involving one-bond formation [7a,b], (2) cyclizations involving formation of two bonds [7a,c], and (3) cyclizations involving formation of three bonds [7a,d–h]. Solid-phase organic synthesis is another synthetic route to these compounds, which has been recently developed [8–10]. Furthermore, a stepwise method toward some antituberculosis 2-phenylamino-5-phenyl-1,3,4-thiadiazoles (the main targets of the present work) has also been reported in the literature [6f]. Considering the green chemistry principles, [11] most of these methods suffer from some limitations, such as using volatile and hazardous organic

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solvents, harsh reaction conditions, and stepwise synthetic protocols, requiring laborious and time-consuming purification of intermediates and more importantly, low to moderate yields of products.

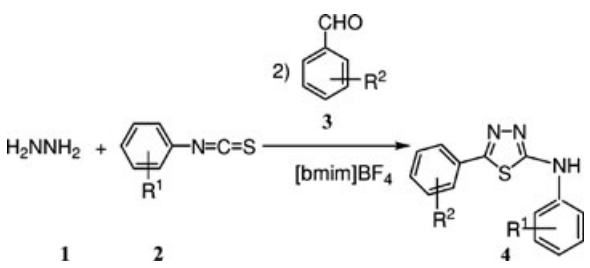
Very recently, the use of room temperature ionic liquids (RTILs) as green solvents for organic synthesis has emerged and gained considerable importance due to their solvating ability, trace to negligible vapor pressure, easy recyclability, and repeated reusability [12]. Among ionic liquids, those with the Brønsted acidity such as 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4) have attracted further interest because of their dual solvent and catalyst role in promoting organic processes [13].

According to the vast number of applications and the environmental demands, search for new methods to replace the commonly known catalysts is one of our targets to provide a greener synthetic methodology. Most of the methods reported in the literature including cyclization need to be catalyzed with acidic (the Brönsted or Lewis) catalysts [8,10]. So, in our investigation to provide a green protocol toward 1,3,4-thiadiazoles, the Brönsted acidic ionic liquid, [bmim]BF_4 (one of the most important room temperature ionic liquids), was chosen as both the reaction medium and promoter.

RESULTS AND DISCUSSION

Scheme 1 shows the course of the process applied for the efficient synthesis of antituberculotic 1,3,4-thiadiazoles under one-step and one-pot reaction condition.

The one-pot three component condensation reaction of hydrazine hydrate with phenylisothiocyanates and benzaldehydes, in the presence of small amounts of 1-butyl-3-methylimidazolium salts ([bmim]X, X = Br, PF_6, BF_4), easily produced 1,3,4-thiadiazoles **4** in high yields in the absence and/or the presence of an added catalyst (comparative results are given in Table 1). To study the scope and limitations of the reaction, some other green conditions



SCHEME 1

TABLE 1 Evaluation of Other Green Reaction Conditions for the Synthesis of Compound **4a**

Medium	*Catalyst*	*Temperature (°C)*	*Time (h)*	*Yield (%)*
TBAB	–	100	>10	10
TBAB	$NaHSO_4$	70	>5	20
TBAB	Na_2HPO_4	70	>5	20
[bmim]PF_6	–	50	3	50
[bmim]BF_4	–	30	0.5	85
[bmim]Br	–	100	>10	15

TBAB: Tetra -*n*-butylammonium bromide.

were considered. In the case of [bmim]Br (tetra-*n*-butylammonium bromide (TBAB)), two mild, safe, green salts, $NaHSO_4$ and NaH_2PO_4, were used as an extra catalyst in this study. The best result was obtained within 10–30 min when [bmim]BF_4 was used as a solvent and catalyst at 30–40°C. The results are summarized in Table 2. The products were obtained in relatively short reaction time, and no impurities were observed by TLC. Using simple workup, the products were then isolated and no further chromatographic purifications were performed because no impurities were observed by NMR.

Excellent isolated yields and short reaction times, as shown in Table 2, clearly indicate the efficiency and versatility of ionic liquid [bmim]BF4 for the synthesis of substituted 2-phenylamino-5-phenyl-1,3,4-thiadiazole derivatives. Repeating the experiment showed that even after third run and measuring reaction time and yield, ionic liquid's activity did not show any significant decrease (Table 3).

The reason for dual catalysis and mediation of [bmim]BF_4 for this reaction can be elicited by comparison of the results in Tables 1 and 2. Reactions were carried out in the ionic liquids without any extra catalyst, and the rates of reactions are remarkably high. Also, the lack of catalytic effect while reaction was run in TBAB without any catalyst (knowing that this kind of ionic liquid is not acidic itself) clearly suggests the catalytic role of the ionic liquid chosen. This enhanced reactivity in imidazolium ionic liquids may be attributed to the inherent Brönsted and Lewis acidity of the ring hydrogens H2, H4, and H5 of the imidazolium cation. Previous studies involving multinuclear NMR spectroscopy and conductivity measurements for the imidazolium ions correlating their acidity characteristics support the above observations [14]. Furthermore, hydrogen bonding between ion pair of [bmim]BF_4, proved by NMR [15] and theoretical studies [16], can also be another important explanation for the reactivity and rate acceleration observed. According to these studies, the

TABLE 2 Results of the Reaction Specified in Scheme 1

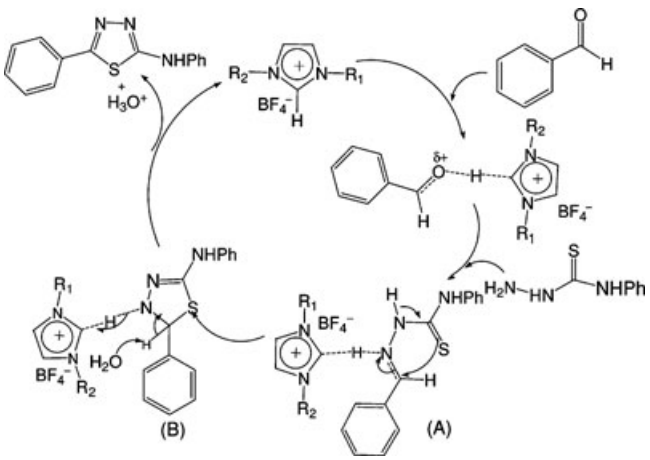
Entry	*R^1*	*R^2*	*Reaction Time (min)*	*Yield[a] (%)*	*M. P. (°C) (Lit.) [Ref.]*
4a	H	H	30	85	200–202 (199–200) [6f]
4b	H	4-Br	20	95	320–323 (338–339) [6f]
4c	H	4-Cl	20	92	217–219 (216–217) [6f]
4d	H	4-F	20	87	252–254 (258–262) [6f]
4e	H	4-NO_2	15	93	267–269 (275–277) [6f]
4f	4-NO_2	H	30	90	207–211 (216–220) [6f]
4g	4-NO_2	4-Br	20	95	281–284 (293–294) [6f]
4h	4-NO_2	4-Cl	20	92	288–290 (300–302) [6f]
4i	4-NO_2	4-NO_2	15	90	343–347 (368) [6f]
4j	4-Me	H	25	80	177–179 (176–180) [6f]
4k	4-Me	4-Cl	15	89	220–224 (213–214) [6f]
4l	4-Me	4-F	15	86	203–207 (210–214) [6f]
4m	4-Me	4-NO_2	10	90	270–273 (280–284) [6f]
4n[b]	3-Me	H	25	95	180–182

[a]Isolated yield.
[b]New compound.

TABLE 3 Reusability of [bmim]BF_4 Ionic Liquid for the Synthesis of Compound **4a**

Run No.	*Yield of **4a** (z)*
1	85
2	82
3	80

ionic liquid [bmim]BF_4 has two strong intramolecular hydrogen bonds between its cation and anion [15,16]. This kind of hydrogen bonding can be disrupted by solutes possessing sites capable of making such bonds. The proposed mechanism is represented in Scheme 2 to further illustrate the possible role of hydrogen bonds in catalyzing and accelerating this reaction.



SCHEME 2

In this proposed mechanism, it can be observed that after formation of 4-phenylthiosemicarbazide, the ionic liquid amplifies the partial positive charge on carbon in the carbonyl group, producing thiosemicarbazone intermediate (A). Then, the ionic liquid accelerates the cyclization to form a cyclic intermediate (B) in the next step, followed by aromatization to the final 1,3,4-thiadiazole product, affecting its activity and the rate enhancement role in this process.

In conclusion, we have developed a new and efficient method for the one-pot synthesis of 1,3,4-thiadiazoles in excellent, isolated yields and short reaction times, using a room temperature ionic liquid, viz. [bmim]BF_4, as a reaction medium. More importantly, the ionic liquid acts not only as a solvating medium but also as a promoter and catalyst for the reaction, giving rise to advantage of both mild temperature conditions and the non-requirement of a catalyst. Easy workup, the absence of a catalyst, and short reaction times in the non-volatile ionic liquid used as the reaction medium make the method amenable for scale-up operations.

EXPERIMENTAL

Melting points were measured on a Buchi B-540 apparatus and are uncorrected. IR spectra were measured on Bomem FTIR ABB FTLA200-100 spectrometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-300 Avance spectrometer at 300 and 75 MHz, using TMS as an internal standard. Chemical shifts are reported (δ) relative to TMS, and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a high resolution Agilent

technology EX mass spectrometer. Chemicals were obtained from Merck Darmstadt, Germany and Sigma-Aldrich Saint Quentin Falavier, Cedex, France and were used without further purification.

General Procedure for the Synthesis of 1,3,4-Thiadiazoles in [bmim]BF_4 Ionic Liquid

Hydrazine hydrate (1 mmol) was added dropwise to substituted phenylisothiocyanate (1 mmol) dissolved in appropriate amount of ionic liquid (1–2 mL), then, only after 5–10 min (monitored by TLC), the substituted benzaldehyde (1 mmol) was added, and the reaction mixture was stirred at 30–40°C until completion (once again as monitored by TLC). After completion of reaction, water was added to the reaction mixture and stirred for 30 min at ambient temperature. Then, the precipitated product was isolated with a simple filtration and recrystallized from ethanol or methanol. The ionic liquid was recovered with evaporation of water in vacuo and reused three times.

Analytical Data for Substituted 1,3,4-Thiadiazoles

2-Phenylamino-5-phenyl-1,3,4-thiadiazole (**4a**). IR (cm^{-1}): 3297 (NH), 3148 (NH), 1606 (C=N), 680 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.21 (t, 1H, $J = 9.0$, para to thiadiazole ring), 7.41 (m, 4H, ortho to thiadiazole ring), 7.57 (d, 2H, $J = 9.0$, meta to thiadiazole ring), 7.90 (m, 2H, meta to thiadiazole ring), 8.17 (s, 1H, ortho to thiadiazole ring), 10.12 (1H, NH), 11.84 (1H, NH).

2-Phenylamino-5-(4-bromophenyl)l-1,3,4-thiadiazole (**4b**). IR (cm^{-1}): 3302 (NH), 3122 (NH), 1595 (C=N), 679 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.21 (t, 1H, $J = 6.5$, para on thiadiazole ring), 7.37 (t, 2H, $J = 6.5$, meta to thiadiazole ring), 7.60 (m, 4H, meta to thiadiazole ring), 7.88 (m, 2H, meta to thiadiazole ring), 8.12 (s, 1H, ortho to thiadiazole ring), 10.17 (1H, NH), 11.88 (1H, NH).

2-Phenylamino-5-(4-chlorophenyl)-1,3,4-thiadiazole (**4c**). IR (cm^{-1}): 3306 (NH), 3132 (NH), 1586 (C=N), 690 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.30 (t, 1H, $J = 6.9$), 7.42 (m, 4H), 7.65 (t, 4H, $J = 7.5$), 7.98 (bs, 1H), 9.18 (s, 1H), 10.47 (s, 1H).

2-Phenylamino-5-(4-fluorophenyl)-1,3,4-thiadiazole (**4d**). IR (cm^{-1}): 3322 (NH), 3132 (NH), 1606 (C=N) 690 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.19 (t, 1H, $J = 6.0$), 7.25 (t, 2H, $J = 6.0$), 7.36 (t, 2H, $J = 9.0$), 7.56 (d, 2H, $J = 6.0$), 7.98 (m, 2H), 10.12 (s, 1H, NH).

2-Phenylamino-5-(4-nitrophenyl)-1,3,4-thiadiazole (**4e**). IR (cm^{-1}): 3347 (NH), 3137 (NH), 2978 (CH), 1596 (C=N), 695 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.1 (t, 1H, $J = 7.5$), 7.40 (t, 2H, $J = 7.5$), 7.77 (d, 2H, $J = 8.4$), 8.18 (d, 2H, $J = 8.4$), 8.38 (d, 2H, $J = 8.4$).

2-(4-Nitrophenylamino)-5-phenyl-1,3,4-thiadiazole (**4f**). IR (cm^{-1}): 3311 (NH), 3154 (NH), 2980 (CH), 1601 (C=N), 690 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.44 (m, 3H), 7.91 (m, 2H), 8.06 (d, 2H, $J = 9.0$), 8.40 (d, 2H, $J = 9.0$), 10.42 (s, 1H, NH).

2-(4-Nitrophenylamino)-5-(4-bromophenyl)-1,3,4-thiadiazole (**4g**). IR (cm^{-1}): 3301 (NH), 3147 (NH), 3003 (CH), 1598 (C=N), 695 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.71 (d, 2H, $J = 8.1$), 7.82 (d, 2H, $J = 8.1$), 8.15 (m, 2H), 8.69 (br. s, 2H), 10.47 (br. s, 1H, NH).

2-(4-Nitrophenylamino)-5-(4-chlorophenyl)-1,3,4-thiadiazole (**4h**). IR (cm^{-1}): 3311 (NH), 3167 (NH), 3014 (CH), 1611 (C=N), 690 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 7.51 (d, 2H, $J = 9.0$), 7.95 (d, 2H, $J = 9.0$), 8.04 (d, 2H, $J = 9.0$), 8.24 (d, 2H, $J = 9.0$), 10.45 (s, 1H, NH).

2-(4-Nitrophenylamino)-5-(4-nitrophenyl)-1,3,4-thiadiazole (**4i**). IR (cm^{-1}): 3302 (NH), 3128 (NH), 2990 (CH), 1596 (C=N), 695 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 8.02 (d, 2H, $J = 9.0$), 8.19 (d, 2H, $J = 9.0$), 8.24 (d, 2H, $J = 4.2$), 8.28 (d, 2H, $J = 4.2$), 10.47 (br. s, 1H, NH).

2-(4-Methylphenylamino)-5-phenyl-1,3,4-thiadiazole (**4j**). IR (cm^{-1}): 3260 (NH), 3200 (NH), 1615 (C=N), 699 (C–S–S); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.27 (s, 1H, CH_3), 2.30 (s, 2H, CH_3), 7.15 (m, 2H para to thiadiazole ring), 7.41 (m, 4H, meta to thiadiazole ring), 7.89 (ortho to thiadiazole ring), 8.14 (s, 1H, ortho to thiadiazole ring), 10.04 (1H, NH).

2-(4-Methylphenylamino)-5-(4-chlorophenyl)-1,3,4-thiadiazole (**4k**). IR (cm^{-1}): 3342 (NH), 3142 (NH), 2978 (CH), 1596 (C=N), 685 (C—S—C); ^{1}H NMR (300 MHz, DMSO-d_6, δ): 2.30 (s, 3H, CH_3), 7.16 (d, 2H, $J = 8.1$), 7.39 (d, 2H, $J = 8.1$), 7.46 (d, 2H, $J = 6.9$), 7.93 (d, 2H, $J = 6.9$), 10.08 (s, 1H, NH).

2-(4-Methylphenylamino)-5-(4-fluorophenyl)-1,3,4-thiadiazole (**4l**). IR (cm^{-1}): 3322 (NH) 3132 (NH) 1606 (C=N) 690 (C—S—C); ^1H NMR (300 MHz, DMSO-d_6, δ): 2.30 (s, 3H, CH_3), 7.16 (d, 2H, $J = 8.1$), 7.39 (d, 2H, $J = 8.1$), 7.56 (d, 2H, $J = 6.0$) 7.98 (m, 2H), 10.12 (s, 1H, NH).

2-(4-Methylphenylamino)-5-(4-nitrophenyl)-1,3,4-thiadiazole (**4m**). IR (cm^{-1}): 3306 (NH), 3126 (NH), 2988 (CH), 1591 (C=N), 690 (C—S—C); ^1H NMR (300 MHz, DMSO-d_6, δ): 2.31 (s, 3H, CH_3), 7.18 (d, 2H, $J = 8.4$), 7.39 (d, 2H, $J = 8.4$), 8.18 (d, 2H, $J = 9.0$), 8.23 (d, 2H, $J = 9.0$).

2-(3-Methylphenylamino)-5-phenyl-1,3,4-thiadiazole (**4n**). IR (cm^{-1}): 3312 (NH), 3163 (NH), 1602 (C=N), 699 (C—S—C); ^1H NMR (300 MHz, DMSO-d_6, δ): 2.32 (s, 3H, CH_3), 7.01 (d, 1H, $J = 6.9$, para to thiadiazole ring), 7.24 (t, 1H, $J = 6.9$, para to thiadiazole ring), 7.42 (m, 5H, meta and ortho to thiadiazole ring), 7.90 (m, 2H, ortho to thiadiazole ring), 8.16 (s, 1H, ortho to thiadiazole ring), 10.04 (1H, NH), 11.8 (1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6, δ): 21.26, 123.12, 126.23, 126.44, 127.91, 128.14, 128.92, 130.30, 134.34, 137.60, 139.26, 143.12, 176.28; MS $m/z = 267$.

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