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Aqueous-Phase Synthesis of 2-Aminothiazole and 2-Iminothiazolidine Derivatives catalyzed by Diammonium Hydrogen Phosphate and DABCO

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Abstract: 2-Aminothiazole and 2-iminothiazolidine derivatives were synthesized from the reaction of phenacyl bromide, thiourea, and its derivatives in aqueous media catalyzed by diammonium hydrogen phosphate (10%) and DABCO (10%) at room temperature in an efficient and simple procedure.

Keywords: 2-Aminothiazole, aqueous media, DABCO, diammonium hydrogen phosphate, 2-iminothiazolidine, phenacyl bromide, thiourea

INTRODUCTION

One of the main aims of green chemistry is the reduction of the use of organic solvents because of the economical and environmental concerns associated with them. Recently, organic reactions in aqueous media have been of interest in organic synthesis.[1] In this article, we describe a user-friendly method for the synthesis of the thiazole ring system, which is a useful structure motif found in numerous biologically active molecules.[2] This structure has found applications in drug development for treatment of allergies,[3] hypertension,[4] schizophrenia,[5] inflammations,[6] and bacterial[7] and HIV[8] infections. The 2-aminothiazole ring is a useful structural element in medicinal chemistry. Aminothiazoles are known to be ligands of esterogen receptors[9] as well as a novel class of adenosine

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receptor antagonists,[10] whereas other analogs are used as fungicides, for in vivo growth of *xanthomonas*, and as an ingredient of herbicidesor as schistosomicidal and anthelmintic drugs.[11] There are some methods for the synthesis of thiazole derivatives based on reaction of phenacyl bromide and thiourea in organic solvents such as DMF[12] and 1,4-dioxane or using solid supports.[13]

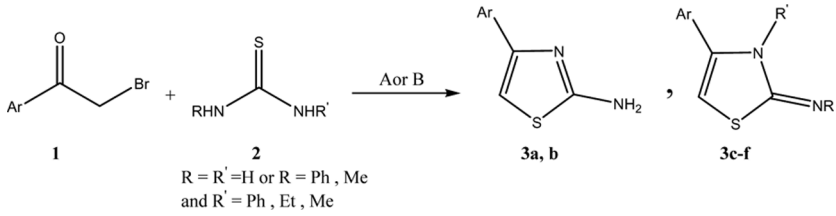
Recently, synthesis of thiazole ring was reported in aqueous media in the presence of β-cyclodextrin at 50 °C.[14] All of the reported methods have some disadvantages such as high temperatures, long reaction times, use of hazardous solvents, and requirements for cleavage of the solid support using acids.

Following our research work to find novel natural catalysts[15] and also to overcome some of the drawbacks in the existing methodologies, we report here the synthesis of 2-aminothiazole and 2-iminothiazolidine derivatives in aqueous media catalyzed by 10% diammonium hydrogen phosphate or DABCO (10%) (Scheme 1).

RESULTS AND DISCUSSION

Reaction of phenacyl bromide and thiourea in aqueous media catalyzed by diammonium hydrogen phosphate (10%) (method A) or DABCO (10%) (method B) leads to 2-amino thiazole (Table 1, entries 1, 2). Meanwhile, unsymmetric *N,N′*-disubstituted thiourea derivatives were synthesized by reaction of phenylisothiocyanate and primary amines. Reaction of *N,N′*-disubstituted thiourea with phenacyl bromide leads to iminothiazolidine derivatives.

Diammonium hydrogen phosphate is a water-soluble catalyst and has been used in the synthesis of heterocyclic compounds[16,17] and alkenes.[17a] Diammonium hydrogen phosphate $(NH_4)_2HPO_4$ is a very cheap, nontoxic, and water-soluble salt whose pH in aqueous solution (1 g/100 ml) is in the range of 7.6–8.4. This reagent has been used in



Scheme 1. (a) $(NH_4)_2HPO_4$ 10% mol, EtOH–H_2O, rt, 30 mins; (b) DABCO 10% mol, ETOH–H_2O, rt, 30 min.

Table 1. Synthesis of 2-aminothiazole and 2-iminiothiazoline derivatives catalyzed by diammonium hydrogen phosphate and DABCO in aqueous media

Entry	Ar	R	R′	Product	Yield (%) (A)[a]	Yield(%) (B)[a]
1	C_6H_5	H	H	3a	87	96
2	4-br-C_6H_4	H	H	3b	98	97
3	C_6H_5	CH_3	CH_3	3c	70	55
4	C_6H_5	Ph	CH_3	3d	85	87
5	C_6H_5	Ph	C_2H_5	3e	76	76
6	C_6H_5	Ph	Ph	3f	86	85

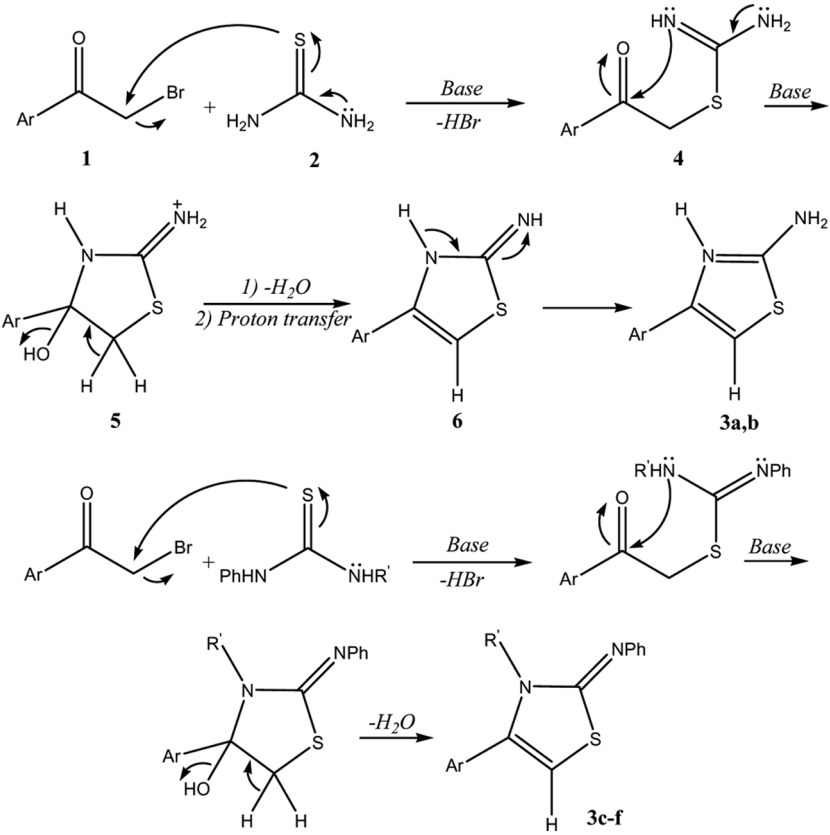
[a]In all cases, the yields are related to pure isolated compounds.

the manufacturing of many important materials such as fireproof textiles, paper, wood, and vegetable fibers.[18] It has also been used as a corrosion inhibitor and fertilizer.[19] Diammonium hydrogen phosphate is a commercially available compound that can be used in the laboratory without any special precaution. DABCO is the most commonly used catalyst in the Baylis–Hillman reaction.[20]

Table 1 summarizes the results of our study. The structures of compounds were deduced from their elemental analysis and their IR and ^{1}H NMR spectra. For example, ^{1}H NMR of **3c** exhibited two singlets identified as methyl (δ 3.06 and 3.42 ppm) and an =CH proton along with singlet (δ 7.10 ppm) and multiplets at δ 7.52 ppm for the aromatic protons. Diammonium hydrogen phosphate and DABCO in catalytic amounts can provide a basic solution that activates thiourea and its derivatives to react with phenacyl bromide in aqueous media at room temperature.

A proposed mechanism for the reaction is outlined in Scheme 2. Based on this mechanism, the basic media provided by DABCO and diammonium hydrogen phosphate in aqueous media makes the assumption reasonable that thiourea is activated in basic media and could be added to phenacyl bromide. The intermediate **4** could be activated and cyclized to compound **5**, which could be converted to our desired product **3a, b** after dehydration and proton transfer. A similar mechanistic trend is suggested for the reaction of unsymmetric *N,N′*-disubstituted thiourea and phenacyl bromide, which is shown in Scheme 2.

In conclusion, we have introduced here a new method for the synthesis of 2-aminothiazole and 2-iminothiazolidine derivatives that can be promoted by DABCO and diammonium hydrogen phosphate in aqueous media at room temperature. Easy workup, short reaction times,



Scheme 2. Proposed mechanism for the synthesis of 2-aminothiazole and 2-iminodihydrothiazole derivatives catalyzed by DABCO or diammonium hydrogen phosphate in aqueous media.

high yields, and environmentally friendliness are advantages of our method over previously reported methods.

EXPERIMENTAL

Melting points were recorded on an Electrothermal 9100 melting-point apparatus and are uncorrected. IR spectra were recorded on a FT-IR Perkin-Elmer GX spectrophotometer using KBr disks. ^{1}H NMR spectra were recorded on Bruker DRX-300 and DRX-500 Avance spectrometer at 300 and 500 MHz in DMSO-d_6 using TMS as the internal standard. Elemental analyses (C, H, N) were performed using a Heraeus CHN Rapid analyzer.

General Procedure for the Synthesis of Compounds 3a–f

Method A

A solution of phenacyl bromide (1 mmol, 199 mg), thiourea or disubstituted thiourea (1.2 mmol), and diammonium hydrogen phosphate (14 mg, 10%) in a 20-ml solution of water–ethanol (1:1) was stirred at room temperature for 30 min. The progress of reaction was monitored by thin-layer chromatography (TLC, eluent: ethyl acetate). The precipitate was collected and washed with water. The crude products were purified by crystallization from EtOH.

Method B

A solution of phenacyl bromide (1 mmol, 199 mg), thiourea or disubstituted thiourea (1.2 mmol), and DABCO (11 mg, 10%) in a 20-ml solution of water-ethanol (1:1) was stirred at room temperature for 30 min. The progress of reaction was monitored by TLC (eluent: ethyl acetate). The precipitate was collected and washed with water. The crude products were purified by crystallization from EtOH.

Selected Data for Compounds 3a–f

Compound 3a: 2-amino-4-phenylthiazole; mp 150–151 °C (151–152 °C)[21]; IR (KBr, cm^{-1}): 3434, 1618, 1519; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.90 (d, 1H, $J = 2.8$ Hz, =CH), 7.05 (s, 2H, NH_2), 7.23 (t, 1H, $J = 6.3$ Hz, H-Ar), 7.34 (t, 2H, $J = 6.9$ Hz, H-Ar), 7.78 (d, 2H, $J = 7.5$ Hz, H- Ar).
Compound 3b: 2-amino-4-(4-bromophenyl)-thiazol; mp 179–181 °C (180–181°C)[22]; IR (KBr, cm^{-1}): 3425, 1636, 1617, 1533; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 7.09 (s, 1H, =CH), 7.11 (s, 2H, NH_2), 7.55 (d, 2H, $J = 7.5$ Hz , H- Ar), 7.74 (d, 2H, $J = 7.5$ Hz, H-Ar).
Compound 3c: N-(3-methyl-4-phenylthiazol-2(3H)-ylidene) methan amine; mp 156–157 °C, IR (KBr, cm^{-1}): 1638, 1618; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.06 (s, 3H, CH_3), 3.42 (s, 3H, CH_3), 7.10 (s, 1H, =CH), 7.52 (m, 5H, H-Ar), 9.87 (s, NH), $C_{11}H_{12}N_2S$ calcd. C, 64.67; H, 5.92; N, 13.71; S, 15.69, Found: C, 64.55; H, 6.61; N, 13.64; S, 15.52.
Compound 3d: N-(3-methyl-4-phenylthiazol-2(3H)-ylidene) phenyl amine; mp 169–170 °C; IR (KBr, cm^{-1}): 1610, 1579; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 3.28 (s, 3H, CH_3), 6.22 (d, 2H, J = 0.93 Hz, =CH), 7.01 (t, 3H, J = 7.35 Hz, Ar), 7.33 (t, 2H, J = 7.26 Hz, Ar), 7.50 (s, 5H, Ar).

$C_{16}H_{14}N_2S$ calcd. C, 72.15; H,5.30; N, 10.52; S, 12.04 Found: C, 71.90, H, 5.41; N, 10.46; S, 12.10.

Compound 3e: N-(3-ethyl-4-phenylthiazol-2(3H)-ylidene) phenyl amine; mp 72 °C; IR (KBr, cm^{-1}): 1616, 1555; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 1.1 (t, 3H, J = 6.92 Hz, CH_3), 3.8 (q, 2H, J = 6.92 Hz, CH_2), 6.17 (s, 1H, =CH), 7.01 (t, 3H, J = 7.74 Hz, Ar), 7.33 (t, 2H, J = 7.56 Hz, Ar), 7.5 (m, 5H, Ar). $C_{17}H_{16}N_2S$ calcd. C, 72.82; H, 5.75; N, 9.99; S, 11.44, Found: C, 72.73; H, 5.71; N, 9.99; S, 11.30.

Compound 3f: N-(3,4-diphenylthiazol-2(3H)-ylidene) phenyl amine; mp 192–193 °C; IR (KBr,cm^{-}): 1617, 1578; ^{1}H NMR (500 MHz, DMSO-d_6) δ: 6.49 (s, 1H, =CH), 6.92 (d, 2H, J = 7.45 Hz, H-Ar), 7.02 (t, 1H, J = 7.36 Hz, H-Ar), 7.16 (m, 2H,H-Ar), 7.24 (m, 3H, H-Ar), 7.29 (m, 5H, H-Ar), 7.36 (t, 2H, J = 7.46 Hz, H-Ar). C $_{21}H_{16}N_2S$ calcd. C, 76.78; H, 4.90; N, 8.53; S, 9.76, Found: C, 76.38; H, 5.10; N, 8.41; S, 9.60.

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