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REMARKABLY FAST AND MILD CONVERSION OF PHENACYL BROMIDE INTO 2-AMINOTHIAZOLE CATALYZED BY MOLECULAR IODINE AT AMBIENT TEMPERATURE CONDITIONS

Shrinivas S. Kottawar, Taterao M. Potewar, Santosh V. Goswami and Sudhakar R. Bhusare*

Department of Chemistry, Dnyanopasak College, Parbhani-431401, MS, India
E-mail: bhusare71@gmail.com

Abstract:
An efficient, simple and green procedure for the synthesis of 2-aminothiazoles is described. The condensation of phenacyl bromide with thiourea and its derivatives using molecular iodine as a green reaction media at ambient temperature affords the title compounds in excellent isolated yields and in a short reaction time.

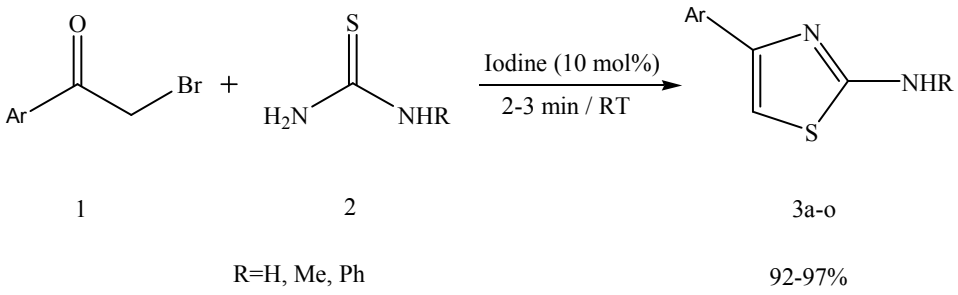
Keywords: 2-Aminothiazole, Ambient temperature, Molecular iodine, Thiourea, Phenacyl bromide.

Introduction

Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. For example, the thiazolium ring present in vitamin B1 (thiamine)[i], carboxylase and penicillin. These heterocyclic systems have found broad applications in drug development for the treatment of HIV infections,[ii] bacterial,[iii], inflammations,[iv] hypertension[v] and anti-cancer.[vi] Aminothiazole analogues are used as fungicides, inhibiting *in vivo* growth of Xanthomonas, as an ingredient of herbicides or as schistosomicidal and anthelmintic drugs.[vii] Aminothiazoles are known to be ligands of estrogen receptors[viii] as well as a novel class of adenosine receptor antagonists.[ix]

Consequently, the enormous numbers of procedure have been developed for the construction of thiazole ring. Haloketones and thioamides provide a useful method for the synthesis of thiazoles.[x] Many improved methods have been developed for the synthesis of thiazole by using catalyst such as β-cyclodextrin in water,[xi] ammonium-12-molybdophosphate in methanol,[xii] ionic liquid,[xiii] without catalyst in water[xiv] and solid supported Nafion-H using polyethylene glycol–water solvent system.[xv] Solid supported synthesis has been widely used to generate small organic molecule libraries[xvi] and solution phase preparation of 2-aminothiazole combinatorial libraries have been reported in DMF[xvii] as well as in 1, 4-dioxane.[xviii] However, reported methods are require long reaction times, high temperature, hazardous solvents with low yields often expansive catalysts. In our efforts to develop methodology and also to overcome some drawbacks in the existing methodologies, we report the synthesis of aminothiazole from phenacyl bromides and thiourea in the presence of molecular iodine (**Scheme 1**).

Molecular iodine has received considerable attention in organic and pharmaceutical synthesis due to its inexpensive, non-toxic, and environmentally friendly characteristics.[xix] Iodine has a high tolerance to air as well as moisture and can be easily removed from reaction systems. Moreover, the mild Lewis acidity associated with iodine has lead to its use in various organic transformations in catalytic to stoichiometric amounts. Dimethyl sulfoxide is an important polar aprotic solvent, because of its excellent solvating power, hence frequently used as solvent for chemical reactions.

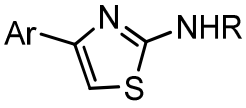


Scheme 1. Synthesis of 2-aminothiazoles

Results and Discussion

Reactions were carried out in dimethyl sulfoxide sequentially addition of phenacyl bromide, thiourea and catalytic amount of iodine to give the corresponding aminothiazole, in impressive yields in just 2-3 minutes (Table 1). In typical experimental procedure iodine was added to a stirred solution of the phenacyl bromide and thiourea in dimethyl sulfoxide at room temperature until completion of the reaction (Progress of reaction was monitored by thin layer chromatography). After completion of reaction the product was extracted by ethyl acetate. Evaporation of solvent gave pure products in excellent yields. The role of iodine is to promote the rate of reaction to completion in decreased reaction times. In absence of iodine, the reaction does take place but the yields were poor (25%) after long reaction time (12-15 h). The structure of (**3a**) was assigned on the basis of ^{1}H and ^{13}C NMR spectral data shows a characteristic peak at δ 6.48 ppm corresponding to the hydrogen of thiazole ring in ^{1}H NMR spectra, while the peak appearing at δ 101.4 and 167.8 ppm corresponds to C-5 and C-2 respectively of the thiazole ring in ^{13}C NMR spectrum.

Table 1. Synthesis of 2-aminothiazoles



Entry	Ar	R	Product	Time (min)	Yield (%)	Mp (°C)
1	C_6H_6	H	3a	2	97	149-150
2	C_6H_6	CH_3	3b	3	95	135-136
3	C_6H_6	C_6H_5	3c	2	97	137-138
4	p-CH_3O-C_6H_5	H	3d	2	92	203-204
5	p-CH_3O-C_6H_5	CH_3	3e	2	94	137-138
6	p-CH_3O-C_6H_5	C_6H_5	3f	3	96	140-141
7	p-F-C_6H_4	H	3g	2	94	103-104
8	p-F-C_6H_4	CH_3	3h	3	94	136-137
9	p-F-C_6H_4	C_6H_5	3i	3	96	111-112
10	m-NO_2-C_6H_5	H	3j	3	97	187-188

11	m- NO_2-C_6H_5	CH_3	3k	2	92	156-158
12	m- NO_2-C_6H_5	C_6H_5	3l	3	92	123-125
13	β-$C_{10}H_7$	H	3m	2	94	151-153
14	β-$C_{10}H_7$	CH_3	3n	3	93	120-122
15	β-$C_{10}H_7$	C_6H_5	3o	2	92	146-147

Experimental

Proton NMR and ^{13}C NMR spectra were recorded with a Bruker AV-200 spectrometer in $CDCl_3$ or DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts (δ) are given from TMS (0 ppm) as internal standard for proton NMR. Infrared spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer using KBr pellets. Elemental analyses were obtained using a flash EA 1112 thermofinnigan instrument. Melting points were recorded in open capillary on Buchi melting point B-540 apparatus. All solvents and chemicals were of research grade and were used as obtained from Merck and Lancaster.

General procedure for synthesis of 2-aminothiazoles (3a-o): A mixture of aromatic α-bromo ketone **1** (1 mmol), thiourea **2** (1.1 mmol) and iodine (0.1 mmol) was stirred in dimethyl sulfoxide (4 ml) at room temperature under vigorous magnetic stirring for the specified time as mentioned in **Table 1**. The progress of the reaction was monitored by thin layer chromatography (pet ether: ethyl acetate 8:2). After completion of the reaction, water (15ml) was added and then product was extracted in ethyl acetate (2 x 15 ml). The organic layer was separated from aqueous layer. The combined organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford the pure product **3** without further purification.

Selected spectral data of the products

4-Phenyl-N-phenylthiazol-2-amine (**3c**): Faint yellow solid; mp 137-138 °C; IR(KBr): 3404, 3019, 1601, 1599, 1541, 1498, 1311, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 6.83 (s, 1H, thiazole H), 7.02-7.11 (m, 1H, ArH), 7.30-7.44 (m, 7H, ArH), 7.49 (bs, 1H, NH), 7.83-7.87 (m, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50MHz): δ 101.6, 118.2, 122.8, 126.1, 127.8, 128.5, 129.3, 134.5, 140.3, 151.2, 164.8; Anal. Calcd for $C_{15}H_{12}N_2S$: C, 71.40; H, 4.79; N, 11.10%. Found: C, 71.54; H, 4.68; N, 11.22%.

4-(4-methoxyphenyl)-N-phenylthiazol-2-amine (3f): Yellow solid; mp 140-141 °C; IR(KBr): 3346, 3019, 2958, 2933, 1668, 1596, 1544, 1487, 1345,757cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 3.84 (s, 3H, OCH3), 6.69 (s, 1H, thiazole H), 6.90-6.95 (d, *J* =8.8 Hz, 2H, ArH), 7.02-7.10 (m, 1H), 7.31-7.41 (m, 5H, ArH), 7.76-7.80 (d, *J* = 8.8 Hz, 2H, ArH); ^{13}C NMR ($CDCl_3$, 50MHz): δ 55.2, 99.9, 113.9, 118.11, 122.8, 127.3, 129.3, 140.3, 150.9, 164.5; Anal. Calcd for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92%. Found: C, 68.19; H, 4.89; N, 10.02%.

4-(4-Fluorophenyl)thiazole-2-amine (3g): Yellow solid; mp 103-104 °C; IR(KBr): 3489, 3019, 1601, 1537, 1490, 1333, 758.cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 5.04 (bs, 2H, NH2), 6.64 (s, 1H, thiazole H), 7.01-7.09(m, 2H, ArH), 7.70-7.77 (m, 2H, ArH);^{13}C NMR ($CDCl_3$, 50MHz): δ 102.1, 115.3, 115.5, 127.6, 130.9, 150.1, 161.3, 163.3, 167.6. Anal. Calcd for $C_9H_7FN_2S$: C, 55.65; H, 3.63; N, 14.42%. Found: C, 55.73; H, 3.56; N, 14.53%.

N-Methyl-4-(3-nitrophenyl)thiazole-2-amine(3k): Orange needles; mp 156-158 °C; IR(KBr) 3431, 3019, 2923, 1591, 1565, 1534, 1517, 1353, 761.cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 3.02-3.04 (d, *J* = 5.12 Hz, 3H, CH_3), 5.39 (bs, 1H, NH), 6.86 (s, 1H, thiazole H), 7.48-7.56 (t, *J* = 7.9 Hz, 1H, ArH), 8.09-8.13 (dd, *J* = 7.9 &1.9 Hz, 2H, ArH), 8.63-8.65 (t, *J* = 1.9 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50MHz): δ=32.1, 103.0, 120.8, 122.1, 129.4, 131.7, 136.5, 148.5, 149.2, 170.8. Anal. Calcd for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86%. Found: C, 51.13; H, 3.77; N, 17.92%.

4-Naphthalen-thiazol-2-amine (3m): Yellow needle; mp 151-153 °C; IR (KBr): 3440, 3019, 1636, 1599, 1534, 1507, 1323, 755.cm^{-1}; ^1H NMR ($CDCl_3$, 200MHz): δ 6.11 (bs, 2H, NH_2),

6.75 (s, 1H, thiazole H), 7.35-7.42 (m, 2H, ArH), 7.70-7.81 (m, 4H, ArH), 8.22 (s, 1H, ArH); ^{13}CNMR ($CDCl_3$, 50MHz): δ 102.0, 123.4, 124.1, 125.2, 125.6, 127.0, 127.4, 127.6131.6, 132.1, 132.9, 150.0, 167.7; Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. %. Found: C, 69.11; H, 4.33; N, 12.47%.

N-methyl-4-(naphthalen-2yl)thiazole-2-amine (3n): Yellow solid; mp 120-122 °C; IR (KBr): 3426, 3019, 2958, 1590, 1560, 1410, 1315, 758cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz): δ 3.02-3.04 (d, J = 5.04 Hz, 3H, CH3), 5.52 (bs, 1H, NH), 6.84(s, 1H, thiazole H), 7.42-7.50 (m, 2H, ArH), 7.77-7.90 (m, 4H, ArH), 8.32 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50MHz): δ 32.2, 101.2, 124.1, 124.9, 125.8, 126.2, 127.6, 128.1, 128.2, 132.3, 132.9, 135.6, 151.64 171.2. Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66%. Found: C, 69.85; H, 5.11; N, 11.71%.

N-phenyl-4-(naphthalen-2yl)thiazole-2-amine (3o): Faint yellow solid; mp 146-147 °C; IR(KBr): 3356, 3019, 1599, 1539, 1496, 1455, 1341, 755.cm^{-1}; ^{1}H NMR ($CDCl_3$, 200MHz): δ 6.95 (s, 1H, thiazole H), 7.04-7.12 (m, 1H, ArH), 7.32-7.52(m, 7H, ArH), 7.80-7.94 (m, 4H, ArH), 8.37 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50MHz): δ 102.3, 118.3, 123.0, 124.0, 125.0, 125.9, 126.2, 127.6, 128.2, 128.3, 129.4, 131.7, 133.0, 133.5, 140.2, 151.2, 164.7; Anal. Calcd for $C_{19}H_{14}N_2S$: C, 75.47; H, 4.67; N, 9.26%. Found: C, 75.52; H, 4.59; N, 9.33%.

Conclusion

In summary, we have successfully employed molecular iodine as an efficient catalyst to promote thiazole ring formation in a short reaction time and excellent yields. Furthermore, the procedure offers several advantages including low cost, simple experimental procedure which make it a useful and attractive strategy in view of economic advantages.

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