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Molecular iodine as a versatile reagent for Hantzsch synthesis of 2-aminothiazole derivatives

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A simple and facile synthesis of 2-aminothiazoles has been accomplished using molecular iodine catalyzed condensation of bromoketones with thiourea. The advantage of this method is that pure products are formed very rapidly under mild conditions.

Keywords: 2-aminothiazoles; molecular iodine; bromoketones; thiourea

1. Introduction

The Hantzsch thiazole synthesis (*1*) is a powerful synthetic tool for the construction of the five membered 2-aminothiazole derivatives. The 2-aminothiazole ring system has been gaining prominence due to the fact that its derivatives have been found to possess a wide spectrum of activities. This structure has found application in drug development for the treatment of allergies (*2*), hypertension (*3*), inflammation (*4*), schizophrenia (*5*), and bacterial (*6*) and HIV (*7*) infections. Recently, it has been utilized for the treatment of pain (*8*) as fibrinogen receptor antagonists with antithrombotic activity (*9*), as inhibitors of bacterial DNA gyrase B (*10*), and in the development of cyclin-dependent kinase inhibitors (*11, 12*). Given this proven utility, it seems reasonable that the development of libraries of 2-aminothiazoles might provide additional lead molecules for use in drug discovery. Various methods have been reported for the preparation of aminothiazoles. The most common method affords the use of α, β-dichloroethyl ethyl ether and thiourea (*13*). Solid-supported synthesis has been used to generate small organic libraries (*14*), and solution-phase preparations of combinatorial libraries have been reported in DMF (*15*), as well as in 1, 4 dioxane (*16*). Nevertheless, these methods suffer from harsh reaction conditions, long reaction times, hazardous solvents and unsatisfactory product yields, which limit their use under the aspect of environmentally benign process. Microwaves have also been used for the preparation of aminothiazoles (*17*), but only small quantities of product can be produced using microwaves, and hence this process is not beneficial industrially.

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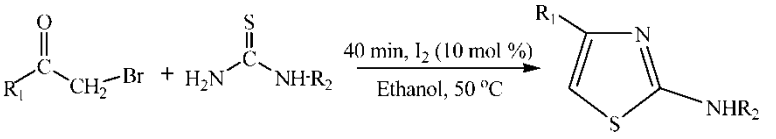


Scheme 1. Synthesis of 2-aminothiazoles from bromoketones and thioureas.

In recent times, the use of molecular iodine has received considerable attention as an inexpensive, non-toxic, readily available catalyst with high tolerance to air and moisture for various organic syntheses to afford the corresponding products in excellent yields with high selectivity (*18*). The mild Lewis acidity (*19, 20*) associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichometric levels to catalytic amounts.

As part of our continuing effort in the laboratory toward the development of new methods for expeditious synthesis of bioactive heterocycles (*21–24*) as well as the usage of iodine for organic transformation (*25–27*), we would like to report a novel and efficient method for the synthesis of 2-aminothiazoles by a condensation of bromoketones and thiourea using molecular iodine as a catalyst (Scheme 1).

2. Results and discussion

At the beginning, a systematic study was carried out for the catalytic evaluation of iodine toward the synthesis of 2-aminothiazoles. Initially, a non-catalyzed condensation of phenacyl bromide **1a** and thiourea **2** had been carried out in boiling ethanol, and the product was obtained after 3 h. The same reaction in the presence of a catalytic amount of molecular iodine (10 mol%) at 50 °C afforded products in an almost quantitative yield within 30 min. Thus, in the absence of a catalyst, the reaction was much slower and required refluxing conditions. Moreover, the product was isolated insignificantly. With these encouraging results in hand, further investigations were carried out for the best reaction conditions.

Different solvents were tried to standardize the reaction condition. Reactions go well with I_2/ethanol, I_2/ethyl acetate and I_2/acetonitrile, but we used only ethanol which is a relatively benign organic solvent. Moreover, with ethanol, only aqueous work up was required, whereas in other solvents, we needed hazardous solvents for the extraction of products. A minimal amount of solvent was required to facilitate homogeneous stirring (Table 1).

Table 1. Effect of solvent on the synthesis of 2-aminothiazole **3a**.[a]

Solvents	Time (min)	Yield (%)[b]
Methanol	40	95
Ethanol	40	98
Diethyl ether	60	94
Acetonitrile	40	96
Ethyl acetate	45	96
Toluene	50	92
Benzene	75	89

Notes: [a]1:1 molar ratio of **1a** and thiourea using 10 mol% of iodine.
[b]Isolated and unoptimized.

Table 2. Influence of the amount of catalyst (I_2) on 2-aminothiazole synthesis.

Iodine (mol%)	Time (min)	Yield (%)[a]
0	3h	76
5	45	96
10	40	97
15	30	98
20	30	98

Note: [a]Isolated and unoptimized.

Table 3. Effect of the temperature on iodine catalyzed aminothiazole[a] synthesis.

Entry	Product	Temperature (°C)	Time (min)	Yield (%)
1.	**3a**	Room temperature	60	96
2.	**3a**	50	40	98
3.	**3a**	60	35	97
4.	**3a**	75	25	98

Note: [a]1:1 molar ratio of **la** and thiourea using 10 mol% of iodine.

To determine the most appropriate reaction conditions, the reaction between phenacyl bromide **1a** and thiourea **2** was examined using different catalytic amounts of iodine. Rate enhancement was observed when higher mole ratios were used, but no significant improvement in the yield was observed (Table 2). Thus, we proceeded with 10 mol% of molecular iodine, so that only a catalytic amount is used.

In order to examine the effect of temperature, the concentration of iodine was kept constant at 10 mol% and the reaction was monitored at different temperatures, as compiled in Table 3. At elevated temperatures, using 10 mol% of iodine gave better results in terms of yield and reaction time.

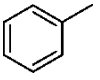
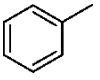
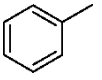
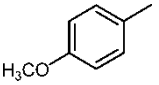
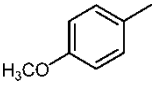
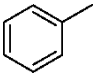
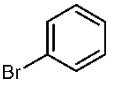
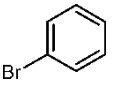
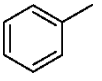
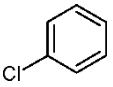
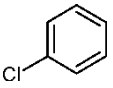
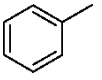
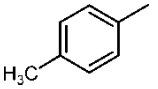
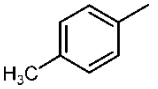
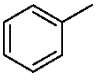
Various phenacyl bromides **1a**–**j** and thioureas exemplify the versatility of this simple protocol (Table 4). The similar reaction between phenacyl bromides and urea to afford the corresponding oxazoles failed under reaction conditions for the synthesis of thiazoles. There was complete conversion and excellent isolated yields were observed for the substrates employed for the synthesis of 2-aminothiazoles. The overall greenness of the reaction was high as a minimal amount of environmentally benign ethanol was used during the course of the reaction. Moreover, it is important to note that in all cases, aminothiazoles were precipitated on dilution of the reaction mixture with water and were isolated by a simple filtration. The dried product, thus obtained, showed a single spot on the TLC and was pure enough for all practical purposes.

From the mechanistic point of view, the first step for the formation of 2-aminothiazole 3 probably involves a nucleophilic attack of thiourea to carbonyl carbon of phenacyl bromide to give an intermediate **c**. The coordination of the carbonyl oxygen with iodine (intermediate **a**) makes the carbonyl carbon more electrophilic and more eligible to the attack of thiourea to give intermediate **b**. Intermediate **c** undergoes deprotonation and the subsequent loss of bromide gives imino intermediate **d** which instantly tautomerizes to product **e** (Scheme 2).

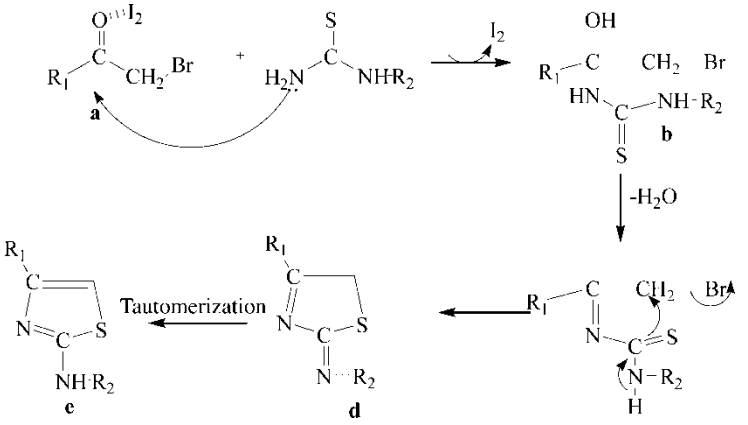
3. Conclusion

A simple and effective synthetic method for 2-aminothiazoles has been developed using cheap, readily available and non-toxic iodine in a catalytic amount.

Table 4. Iodine promoted synthesis of 2-aminothiazoles.[a]

1	R_1	R_2	Product	Time (min)	MP (°C)	Yield (%)[b]
1a		−H	**3a**	40	150–151	98
1b			**3b**	35	136–137	96
1c		−H	**3c**	30	204–205	98
1d			**3d**	35	180–181	97
1e		−H	**3e**	35	165–167	99
1f			**3f**	30	143–144	98
1g		−H	**3g**	40	176–177	96
1h			**3h**	30	152–153	97
1i		−H	**3i**	40	136–137	99
1j			**3j**	35	170–171	97

Notes: [a]Reaction conditions: substituted phenacyl bromide (1 mmol), N-substituted thiourea (1 mmol); iodine (10 mol%); solvent ethanol.
[b]Isolated and unoptimized yields.



Scheme 2. Plausible mechanism of the iodine catalyzed Hantzsch aminothiazole synthesis.

4. Experimental

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer using KBr as pastilles. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance Spectrospin at 300 and 75 MHz, respectively, using TMS as internal standard. Analytical TLCs were performed on pre-coated Merck silica gel 60 F_{254} plates; the spots were detected either under UV light or by placing in iodine chamber. Elemental analysis was performed on a Horeaus CHN rapid analyzer. The temperature of the reaction mixture was measured through a non-contact mini gun thermometer (AZ minigun type, model 8868). X-ray diffraction data were using a Enraf-Nonius CAD4 diffractometer.

4.1. *General procedure for the synthesis of 2-aminothiazoles*

A 50 ml round-bottomed flask was filled with phenacyl bromide **1a**–**h** (1 mmol), thiourea **2** (1 mmol) and iodine (10 mol%) followed by 5 ml of ethanol. The mixture was then stirred at 50 °C until the reaction was complete (TLC). The reaction mixture was treated with aqueous $Na_2S_2O_3$ solution. The solid 2-aminothiazole product that separated out was filtered, then washed with water and dried. The crude product, thus obtained, was subjected to purification by column chromatography on silica gel (60–120 mesh size) using 25% ethyl acetate in petroleum ether as an eluent to yield 2-aminothiazoles, **3a**–**h**. The structures of all products were unambiguously established on the basis of spectral analysis (TR, ^{1}H NMR, ^{13}C NMR, mass spectral data and elemental analysis) and melting point determination (*28–32*). X-ray analysis was carried out for **3f** (Figure 1).

4.2. *X-ray crystallography*

Compound **3f** was prepared by crystallization from the solution of ethanol/chloroform (6:4) under controlled conditions. The details of crystal data, intensity data collection and refinement are given in supplementary data. The DIFABS absorption correction was made. The structure was determined by a direct method using the program SHELXS 97 and difference Fourier calculation. The coordinates of non-hydrogen atoms were refined anisotropically using the program SHELXL

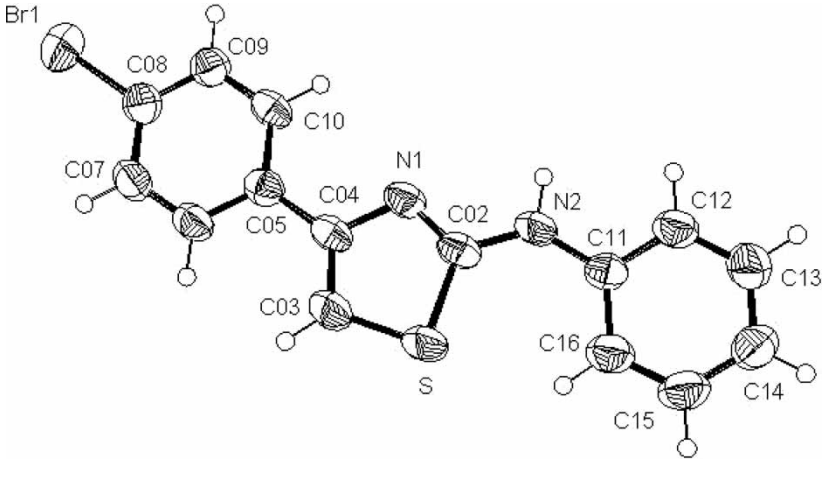


Figure 1. ORTEP view of the compound **3f** at 50% ellipsoidal probability. Crystallographic data for the structure **3f** have been deposited within Cambridge Crystallographic Data Centre as supplementary publication number CCDC 665472.

97 (*33*). The position of hydrogen atoms was determined from difference Fourier maps and was used in the final cycles of refinement using isotropic temperature factors of the non-hydrogen atoms to which they were attached. The final *R*-factor for 2450 observed reflection [$I \geq 2\sigma(I)$] was 0.0503. The atomic scattering factors used in these calculations were those of Cromer and Mann (*34*) for non-atoms and of Stewart et al. (*35*) for hydrogen atoms.

4.3. *Spectral and analytical data for synthesized compounds 3a–j*

4.3.1. *2-Amino-4-phenylthiazole (**3a**)*

IR (cm^{-1}, KBr): 3400, 3260, 1640, 1462, 1377, 765, 653; ^{1}H NMR (MeOH, 300 MHz): δ 3.96 (s, NH_2), 6.7 (s, 1H), 7.22 (m, 1H, Ar–H), 7.32 (m, 2H, Ar–H), 7.48 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 103.4, 127.0, 129.1, 128.5, 150.8, 173.2; HRMS; m/z 176.2415 (M^+); $C_9H_8N_2S$: calcd. C, 61.33; H, 4.57; N, 15.8; found C, 61.24; H, 4.61; N, 15.7.

4.3.2. *2-Phenylamino-4-phenylthiazole (**3b**)*

IR (cm^{-1}, KBr): 3318, 1614, 1463, 1377, 770, 694; ^{1}H NMR (MeOH, 300 MHz): δ 4.0 (s, NH_2), 6.7 (s, 1H), 7.27 (m, 1H, Ar–H), 7.34 (m, 1H, Ar–H), 7.52 (m, 2H, Ar–H), 6.46 (m, 2H, Ar–H), 7.01 (m, 2H, Ar–H), 6.62 (m, 1H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 103.4, 115.1, 118.5, 127.2, 128.5, 129.0, 129.3, 136.5, 146.7, 173.2; HRMS; m/z 252.343 (M^+); $C_{15}H_{12}N_2S$: calcd. C, 71.3; H, 4.8; N, 11.1; found C, 71.1; H, 4.8; N, 11.2.

4.3.3. *2-Amino-4 (4′-methoxyphenyl) thiazole (**3c**)*

IR (cm^{-1}, KBr): 3382, 3269, 1631, 1461, 1259, 850, 723; ^{1}H NMR (MeOH, 300 MHz): δ 3.77 (s, NH_2), 6.74 (s, 1H), 3.73 (s, $-OCH_3$), 6.88 (m, 2H, Ar–H), 7.72 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 54.3, 103.4, 114.2, 128.8, 150.2, 162.2, 173.2; HRMS; m/z 206.268 (M^+); $C_{10}H_{10}N_2SO$: calcd. C, 58.2; H, 4.8; N, 13.6; found C, 58.4; H, 4.7; N, 13.7.

4.3.4. *2-Phenylamino-4 (4′-methoxyphenyl) thiazole (**3d**)*

IR (cm^{-1}, KBr): 3410, 1640, 1461, 1370, 762, 690; ^{1}H NMR (MeOH, 300 MHz): δ 3.82 (s, NH_2), 6.64 (s, 1H), 6.94 (m, 1H, Ar–H), 7.85 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H), 6.62 (m, 1H, Ar–H), 7.2 (m, 1H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 56.0, 103.2, 115.2, 115.3, 118.5, 129.2, 129.3, 144.7, 156.8, 173.2; HRMS; m/z 282.365 (M^+); $C_{16}H_{14}N_2SO$: calcd. C, 68.1; H, 4.9; N, 9.9; found C, 68.2; H, 4.9; N, 9.7.

4.3.5. *2-Amino-4 (4′-bromophenyl) thiazole (**3e**)*

IR (cm^{-1}, KBr): 3372, 3272, 1632, 1458, 1372, 764, 672; ^{1}H NMR (MeOH, 300 MHz): δ 4.0 (s, NH_2), 6.6 (s, 1H), 7.47 (m, 2H, Ar–H), 7.52 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 101.2, 124.2, 129.2, 132.3, 136.5, 152.8, 173.2; HRMS; m/z 255.267 (M^+); $C_9H_7N_2SBr$: calcd. C, 42.3; H, 2.7; N, 11.0; found C, 42.2; H, 2.5; N, 11.2.

4.3.6. *2-Phenylamino-4 (4′-bromophenyl)-thiazole (**3f**)*

IR (cm^{-1}, KBr): 3340, 1617, 1470, 1370, 762, 680; ^{1}H NMR (MeOH, 300 MHz): δ 4.1 (s, NH_2), 6.7 (s, 1H), 7.23 (m, 2H, Ar–H), 7.53 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H), 6.7 (m, 1H, Ar–H), 7.2

(m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 103.2, 114.2, 118.5, 123.1, 128.3, 129.2, 132.4, 137.2, 147.2, 150.8, 174.2; HRMS; m/z 331.362 (M^+); $C_{15}H_{11}N_2SBr$: calcd. C, 54.3; H, 3.3; N, 8.5; found C, 54.4; H, 3.1; N, 8.2.

4.3.7. *2-Amino-4 (4′-chlorophenyl) thiazole (**3g**)*

IR (cm^{-1}, KBr): 3383, 3266, 1627, 1494, 1395, 745, 657; ^{1}H NMR (MeOH, 300 MHz): δ 4.2 (s, NH_2), 6.63 (s, 1H), 7.28 (m, 2H, Ar–H), 7.52 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 102.3, 128.3, 129.8, 133.2, 134.6, 150.2, 173.2; HRMS; m/z 210.814 (M^+); $C_9H_7N_2SCI$: calcd. C, 51.31; H, 3.35; N, 13.30; found C, 51.33; H, 3.32; N, 13.32.

4.3.8. *2-Phenylamino-4 (4′-chlorophenyl) thiazole (**3h**)*

IR (cm^{-1}, KBr): 3400, 1640, 1462, 1377, 765, 653; ^{1}H NMR (MeOH, 300 MHz): δ 3.96 (s, NH_2), 6.7 (s, 1H), 7.22 (m, 1H, Ar–H), 7.52 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H), 6.62 (m, 1H, Ar–H), 7.2 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 104.2, 115.2, 118.5, 128.3, 129.4, 133.8, 134.6, 146.7, 150.8, 173.2; HRMS; m/z 176.2415 (M^+); $C_9H_8N_2S$: calcd. C, 61.33; H, 4.57; N, 15.8; found C, 61.2; H, 4.4; N, 15.5.

4.3.9. *2-Amino-4 (4′-methylphenyl) thiazole (**3i**)*

IR (cm^{-1}, KBr): 3412, 3264, 1632, 1470, 1362, 764, 682; ^{1}H NMR (MeOH, 300 MHz): δ 3.8 (s, NH_2), 6.38 (s, 1H), 2.35 (s, 1H), 7.14 (m, 1H, Ar–H), 7.32 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 21.1, 102.3, 126.9, 129.2, 134.2, 137.7, 173.2; HRMS; m/z 190.326 (M^+); $C_{10}H_{10}N_2S$: calcd. C, 63.1; H, 5.3; N, 14.7; found C, 63.3; H, 5.1; N, 14.7.

4.3.10. *2-Phenylamino-4 (4′-methylphenyl) thiazole (**3j**)*

IR (cm^{-1}, KBr): 3352, 1614, 1462, 1373, 772, 678; ^{1}H NMR (MeOH, 300 MHz): δ 4.2 (s, NH_2), 6.8 (s, 1H), 2.34 (s, 3H, CH_3), 7.12 (m, 2H, Ar–H), 7.38 (m, 2H, Ar–H), 6.42 (m, 2H, Ar–H), 6.62 (m, 1H, Ar–H), 7.1 (m, 2H, Ar–H); ^{13}C NMR (MeOH, 75 MHz): δ 21.1, 102.3, 115.1, 118.3, 127.1, 129.3, 134.2, 137.7, 146.7, 173.2; HRMS; m/z 266.494 (M^+); $C_{16}H_{14}N_2S$: calcd. C, 72.1; H, 5.3; N, 10.6; found C, 72.1; H, 5.4; N, 10.3.

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