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An efficient synthesis of thiazol-2-imine derivatives via a one-pot, three-component reaction

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ABSTRACT

A simple and highly efficient one-pot, three-component procedure for the synthesis of thiazol-2-imines, via the reaction of aromatic α-bromoketones, primary amines, and phenyl isothiocyanate in the presence of a catalytic amount of triethylamine, is described.

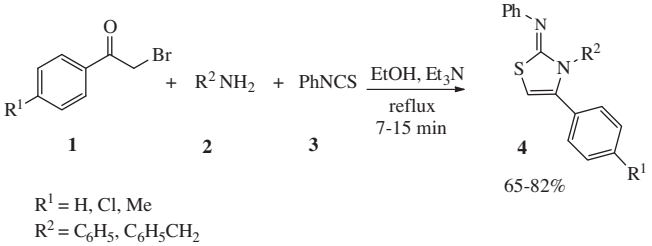
As a result of the convergent character of multi-component reactions (MCRs), several molecules are assembled into the product in one reaction step. Atom economy, simplicity, and time-saving features are the advantages of MCRs for the synthesis of biologically active compounds such as drugs and agricultural chemicals. For these reasons MCRs are important in research.[1,2]

Heterocyclic compounds demonstrate various biological activities in particular, thiazoline derivatives have been applied in agriculture as acricides, insecticides, and plant growth regulators.[3] The thiazol-2-imine ring system has attracted considerable attention due to its presence in several drug candidates with different biological activities[4] such as anti-inflammatory, analgesic and kinase (CDK1, CDK5, and GSK3) inhibition,[5] antifungal,[6] melanin-reducing activity (skin whitening agent),[7] and as platelet GPIIb/IIIa receptor antagonists.[8]

The Hantzsch condensation reaction was the first method employed for the synthesis of 2-aminothiazole moiety using an α-haloketone and thiourea as starting materials.[9] N-alkylated imino-thiazolines could be obtained by replacing thioureas with mono and *N,N*-disubstituted thioureas under different reaction conditions[10] such as in aqueous media catalyzed by diammonium hydrogen phosphate or DABCO,[11] and basic alumina under MW irradiation.[12] Instead of using α-bromoketones in this procedure as one of the starting materials, Murru et al.[13] reported the one-pot reaction of 1,1′-(ethane-1,2-diyl) dipyridinium bistribromide (EDPBT), as a brominating agent, enolizable ketones, and disubstituted thioureas.

Several alternative methods have been devised, which include copper-catalyzed N-phenylation of 2-aminobenzothiazole derivatives,[14] condensation of thiazol-2(3*H*)-imines with 4-chloro and 4-isothiocyanato acridines,[5] cycloaddition of 5-imino-1,2,4-thiazolidin-3-ones with both electrophilic and nucleophilic unsaturated compounds such as enamines and ester enolates,[15] condensation of (2-bromo-1-phenylethylidene)malononitrile and monoalkylated thioureas,[16] ring expansion of 1-aryl methyl-2-(thiocyanatomethyl)aziridine with an acyl chloride in the presence of $TiCl_4$,[17] reaction of *N*-propargylaniline with acylisothiocyanates,[18] potassium thiocyanate with an α-bromoketimine,[19] phenylamino acetonitrile and alkyl isothiocyanate,[20] and many one-pot procedures for the preparation of 2-acylimino thiazoline derivatives.[21]

Due to the biological activity of thiazol-2-imines and our continuing interest in the development of new strategies toward the synthesis of heterocyclic compounds,[22–24] we report a regioselective three-component reaction, between aromatic α-bromoketones **1**,



Scheme 1. Three component synthesis of thiazole-2-imines.

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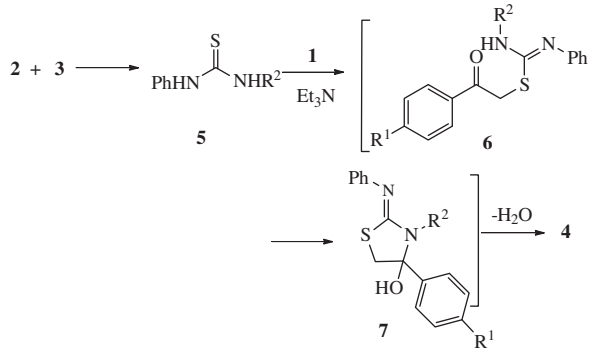
Table 1
Reaction of aromatic α-bromoketones, phenyl isothiocyanate and primary amines

Entry	R^1	R^2	Product	Time (min)	Yield[a] (%)
1	H	C_6H_5	**4a**	9	79
2	H	$C_6H_5CH_2$	**4b**	13	82
3	Cl	C_6H_5	**4c**	10	70
4	Cl	$C_6H_5CH_2$	**4d**	7	65
5	Me	C_6H_5	**4e**	7	77
6	Me	$C_6H_5CH_2$	**4f**	12	72

[a] Isolated yield.



Scheme 2. Plausible mechanism for the formation of thiazole-2-imines.

primary amines **2** and phenyl isothiocyanate **3** in the presence of triethylamine, which leads to thiazol-2-imines **4** in good to excellent yields (Scheme 1). [25]

As summarized in Table 1, the reactions proceed in short times and afford pure products in good to excellent yields, without the need for tedious purification procedures. The structures of the synthesized compounds were fully supported by IR, ^{1}H, and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The previously reported X-ray crystal structure[13] of thiazol-2-imine also confirmed that they have *syn* stereochemistry due to the steric hindrance between the R^2 and *N*-Ph groups.

A proposed mechanism for the reaction is outlined in Scheme 2. Addition of the primary amine to phenyl isothiocyanate affords intermediate **5**. The carbon of the bromomethyl group of **1** is attacked by sulfur to produce **6**, which is facilitated by abstraction of the NH proton. Cyclization and dehydration result in product **4**. The reaction proceeds regioselectively because of the higher acidity of the NH proton flanked by a phenyl group.

A previous mechanistic study[13] suggested that the tertiary hydroxyl in the intermediate from ring closure, is protonated prior to elimination; under our conditions the Et_3N (20 mol %) cannot neutralize all the HBr produced and thus we suggest that acid-catalyzed elimination of water also occurs under our conditions. The reaction was also studied using one equivalent of Et_3N: after cooling the reaction mixture, triethylamine hydrobromide separated and was dissolved in H_2O, however the desired product was obtained in only a low yield.

In conclusion we have described a simple and efficient route for the synthesis of new thiazol-2-imine derivatives via a one-pot, three-component reaction. Short reaction times, good to excellent yields, and the simple experimental procedure are the advantages of this method in comparison to other routes.

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25. *General procedure for the synthesis of N-(3,4-diphenylthiazol-2(3H)-ylidene)phenylamine* (**4a**): To a mixture of aniline (1 mmol) and phenyl isothiocyanate (1 mmol) in EtOH (3 ml) under reflux, was added phenacyl bromide (1 mmol) and Et_3N (0.2 mmol). After heating for the time shown in Table 1 (completion of the reaction was monitored by TLC), the mixture was cooled and the resulting solid filtered and dried to give **4a** as a white powder without further purification (0.26 g, 79%): mp = 189–192 °C. lit.[13] 196–197 °C. IR (KBr) cm^{-1}: 1616, 1576, 1486, 1361, 1246, 1141, 766, 696. ^{1}H NMR (500.1 MHz, $CDCl_3$) δ: 5.97 (1H, s, =CH), 7.04 (2H, d, *J* = 7.7, H-Ar), 7.11 (2H, d, *J* = 7.1, H-Ar), 7.18–7.24 (4H, m, H-Ar), 7.27–7.28 (3H, m, H-Ar), 7.30–7.38 (4H, m, H-Ar). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 97.1, 121.6, 123.2, 127.2, 128.0, 128.6, 128.8, 129.1, 129.8, 130.5, 137.4, 137.9, 139.5, 151.7, 159.9. MS *m/z*: 328 (M^+, 16), 180 (34), 149 (79), 77 (66), 69 (67), 57 (85), 43 (100). Anal. Calcd for $C_{21}H_{16}N_2S$: C, 76.80; H, 4.91; N, 8.53. Found: C, 76.75; H, 4.98; N, 8.39.
Compound characterization Data. N-(3-Benzyl-4-phenylthiazol-2(3*H*)-ylidene)phenylamine (**4b**): white powder (0.28 g, 82%): mp = 156–157 °C. IR (KBr) cm^{-1}: 1618, 1583, 1488, 1321, 1234, 1123, 793, 700. ^{1}H NMR (400.2 MHz, $CDCl_3$) δ: 5.13 (2H, s, CH_2), 5.83 (1H, s, =CH), 7.07–7.14 (5H, m, H-Ar), 7.25–7.30 (5H, m, H-Ar) 7.36–7.45 (5H, m, H-Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 48.5, 95.9, 121.5, 123.0, 127.1, 127.2, 128.3, 128.6, 129.0, 129.1, 129.4, 131.6, 137.5, 140.4, 151.5, 159.9. MS *m/z*: 342 (M^+, 11), 251 (24), 167 (100), 149 (32), 134 (91), 91 (56). Anal. Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.24; H, 5.23; N, 8.30.
N-[4-(4-Chlorophenyl)-3-phenylthiazol-2(3H)-ylidene]-phenylamine (**4c**): white powder (0.25 g, 70%): mp = 277–279 °C. IR (KBr) cm^{-1}: 1606, 1564, 1485, 1349, 1143, 1082, 810, 756, 693.^{1}H NMR (400.2 MHz, $CDCl_3$) δ: 6.01 (1H, s, =CH), 7.05–7.10 (5H, m, H-Ar), 7.19–7.21 (2H, d, *J* = 8.4, H-Ar), 7.28–7.33 (4H, m, H-Ar), 7.35–7.40 (3H, m, H-Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 97.9, 121.6, 123.4, 127.8, 128.5, 128.8, 129.1, 129.3, 129.4, 130.0, 134.3, 137.7, 138.8, 151.6, 159.9. MS *m/z*: 364 (M^+, ^{37}Cl, 9), 362 (M^+, ^{35}Cl, 32), 214 (93), 167 (75), 149 (100), 113 (36), 77 (60), 57 (91). Anal. Calcd for $C_{21}H_{15}ClN_2S$: C, 69.51; H, 4.17; N, 7.72. Found: C, 69.52; H, 4.25; N, 7.63.
N-[3-Benzyl-4-(4-chlorophenyl)thiazol-2(3H)-ylidene]-phenylamine (**4d**): white powder (0.24 g, 65%): mp = 154 °C. IR (KBr) cm^{-1}: 1614, 1582, 1486, 1321, 1231, 1125, 1086, 841, 769, 693. ^{1}H NMR (400.2 MHz, $CDCl_3$) δ: 5.10 (2H, s, CH_2), 5.83 (1H, s, =CH), 7.08–7.18 (7H, m, H-Ar), 7.24–7.40 (7H, m, H-Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 48.6, 96.6, 121.5, 123.2, 127.0, 127.2, 128.5,

128.8, 129.5, 130.0, 130.2, 135.3, 137.3, 139.3, 151.3, 159.8. MS *m/z*: 378 (M^+, ^{37}Cl, 9), 376 (M^+, ^{35}Cl, 25), 285 (28), 167 (100), 149 (36), 91 (92). Anal. Calcd for $C_{22}H_{17}ClN_2S$: C, 70.11; H, 4.55; N 7.43. Found: C, 70.13; H, 4.57; N, 7.39.

N-(3-Phenyl-4-*p*-tolylthiazol-2(3*H*)-ylidene)phenylamine (**4e**): white powder (0.26 g, 77%): mp = 153 °C. IR (KBr) cm^{-1}: 1598, 1549, 1487, 1362, 1171, 1065, 846, 767, 693. ^1H NMR (400.2 MHz, $CDCl_3$) δ: 2.32 (3H, s, CH_3), 5.96 (1H, s, =CH), 7.03–7.08 (7H, m, H-Ar), 7.26–7.39 (7H, m, H-Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 21.2, 96.6, 121.7, 123.2, 127.5, 128.1, 128.81, 128.89, 128.9, 129.0, 129.4, 138.1, 138.2, 140.0, 151.9, 160.3. MS *m/z*: 342 (M^+, 25), 194 (96), 167 (67), 149 (100), 91 (33), 77 (55). Anal. Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18. Found: C, 77.25; H, 5.34; N, 8.09.

N-(3-Benzyl-4-*p*-tolylthiazol-2(3*H*)-ylidene)phenylamine (**4f**): white powder (0.26 g, 72%): mp = 106–108 °C. IR (KBr) cm^{-1}: 1614, 1577, 1451, 1379, 1232, 1119, 1025, 875, 727, 696.^1H NMR (400.2 MHz, $CDCl_3$) δ: 2.41 (3H, s, CH_3), 5.17 (2H, s, CH_2), 5.83 (1H, s, =CH), 7.07–7.20 (9H, m, H-Ar), 7.22–7.30 (3H, m, H-Ar), 7.37 (2H, t, *J* = 7.6, H-Ar). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 21.4, 48.6, 95.8, 121.6, 123.2, 127.1, 127.2, 128.4, 128.6, 128.9, 129.3, 129.5, 137.5, 139.3, 140.7, 151.1, 160.3. MS *m/z*: 356 (M^+, 10), 265 (18), 167 (100), 148 (71), 101 (27), 86 (93). Anal. Calcd for $C_{23}H_{20}N_2S$: C, 77.49; H, 5.65; N, 7.86. Found: C, 77.56; H, 5.57; N, 7.87.