Copper(I) Bromide-Mediated Synthesis of Novel 2-Arylthiazole-5-carboxylates from α-Diazo-β-Keto Esters and Aromatic Thioamides

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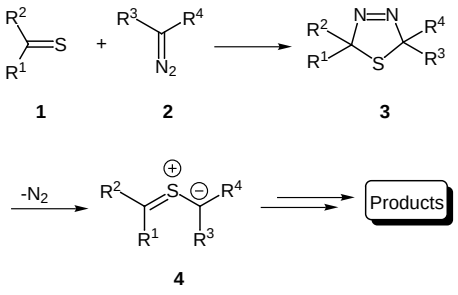
Abstract: Starting from readily available α-diazo-β-keto esters **8** and aromatic primary thioamides **9** and **14**, a simple synthesis of 2-aryl 4-substituted thiazole-5-carboxylate derivatives of type **10** and **16** has been accomplished. The method is based on the efficient catalysis of CuBr, which promotes the formation of the corresponding carbenoids **11** from diazo derivatives **8.** These Cu-carbenoids **11** react with the thiocarbonyl group of the primary thioamides to afford presumably intermediates of the general type **12**, which by subsequent cyclocondensation furnish the title thiazole derivatives.

Key words: thiazoles, primary aromatic thioamides, CuBr catalysis, α-diazo-β-keto esters, carbenoid formation

It is well known that the thiocarbonyl group (C=S) is a very reactive dipolarophile. The reaction between thioketones ("superdipolarophiles")[3,4] and diazo compounds was first studied many years ago by Staudinger.[5] From this seminal work and through the fundamental studies carried out by Schönberg,[6,7] Huisgen[8–10] and others,[11] it was shown that thiocarbonyl compounds **1** react very efficiently with diazo derivatives **2** to give 2,5-dihydro-1,3,4-thiadiazoles of type **3**.[12] Most of these adducts **3**, are rather unstable at ambient temperature and eliminate N_2 spontaneously or after slight warming to give reactive thiocarbonyl ylides of type **4**, which depending on the substitution pattern and/or on the reaction conditions, can undergo various reactions such as 1,3-dipolar cycloadditions,[13–16] ring closure to thiiranes,[17–19] dimerization to 1,4-dithianes,[20,21] 1,4-shifts[22] and 1,5-dipolar electrocyclizations[23] (Scheme 1).



Scheme 1

In addition to their intrinsic theoretical interest, these reactions between thiocarbonyl groups and diazo compounds have also found useful preparative applications in the synthesis of several complex natural products like the antibiotic indolizomycin,[24,25] the alkaloids chilenine and cephalotaxine.[26] In these cases, the formation of the corresponding thiocarbonyl ylides served as the key intermediates for the successful accomplishment of their total syntheses.

During the course of our ongoing studies on the development of efficient methodologies that could readily be adapted for combinatorial and/or parallel synthesis of relevant core structures in solution or on solid supports,[27–31] we became interested in exploring the synthetic possibilities offered by thiocarbonyl ylides specifically generated from primary thioamides, as useful reactive intermediates toward the preparation of different heterocyclic systems.[32]

There are many reports in the literature regarding the use in organic synthesis of thiocarbonyl ylides generated by the reaction of diazo compounds with thioketones,[33] thiolactones,[34,35] and thiolactams,[36] however, the analogous reaction with thioamides has received considerably less attention. Only recently has it been reported that when 2-diazo-1,3-diketones are allowed to react with thioamides at high temperatures, the corresponding condensation products of the 1,3-oxazinone type are formed in good yields together with small amounts of 5-acylthiazoles. The same reaction under photochemical conditions was reported to produce only the corresponding 5-acylthiazole derivatives albeit in low yields.[37]

Herein, we report our findings from an investigation of the reaction between α-diazo-β-keto esters and primary thioamides and its application toward the synthesis of novel thiazole derivatives. We prepared a number of α-diazo-β-keto esters of type **8** using known procedures. These were formed in high yields by the reaction of tosyl azide with β-keto esters **7** in the presence of a suitable base.[38] (***Caution!*** we have routinely worked with derivatives of type **8** in scales up to 5 g and although in our hands no hazard occurred, α-diazo carbonyl compounds are toxic and potentially explosive. Accordingly, they should be handled with care). In turn, commercially unavailable β-keto esters **7** were also prepared easily in high yields by following a one-pot, two-step procedure based on the condensation of different acid chlorides **5** with Meldrum's acid **6** and subsequent alcoholysis[39] (Scheme 2).

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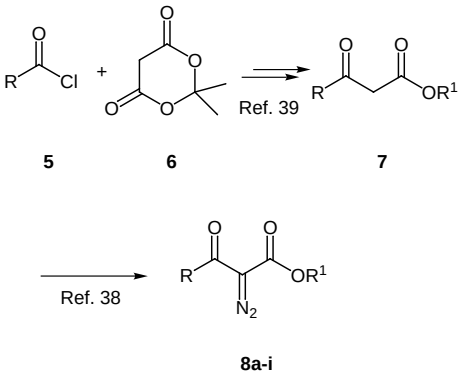
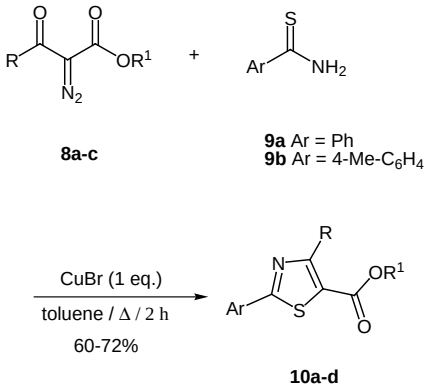


5 6 7

8a-i

Scheme 2



8a-c

10a-d

Scheme 3

Table 1 2-Arylthiazole-5-carboxylates **10a–d** Prepared

Product[a]	Ar	R	R^1	Yield (%)	Mp (°C)
10a	Ph	Ph	Et	78	101–102
10b	Ph	$PhCH_2CH_2$	Et	62	85–86
10c	Ph	Pr	Et	66	105–106
10d	4-MeC_6H_4	Ph	Et	65	94–95

[a] Satisfactory microanalyses obtained: C ± 0.29, H ± 0.33, N ± 0.27, S ±0.25.

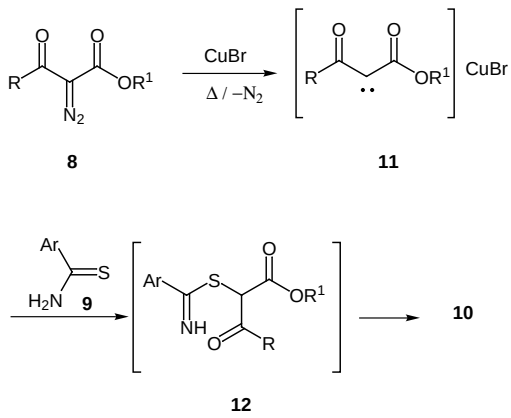
When the diazo derivatives **8** were allowed to react with aromatic primary thioamides **9a**,**b** in refluxing toluene in the presence of 1 equivalent of CuBr for 2 hours, the corresponding thiazole derivatives **10a–d** were obtained in good yields (62–78%) (Scheme 3, Tables 1 and 2).

Apparently, this transformation takes place via the efficient catalytic effect of copper(I), which generates the corresponding carbenoids **11** from **8**. These Cu-carbenoids **11** react with the thiocarbonyl group of **9** to give an intermediate **12**, which, after cyclocondensation, affords trisubstituted thiazoles **10** (Scheme 4).

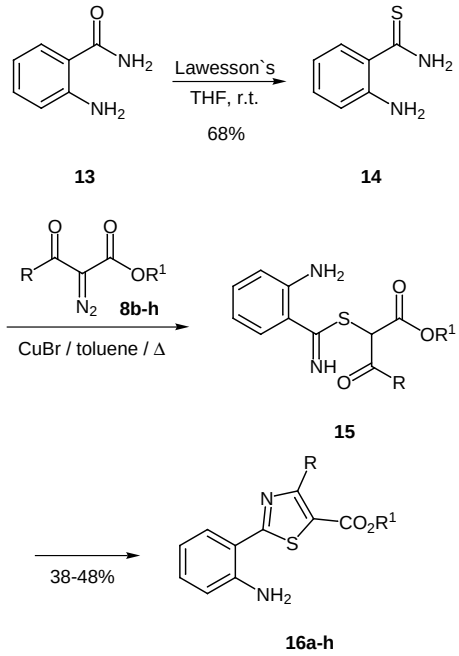
The use of other metals as catalysts, such as $Rh_2(OAc)_4$, led to untreatable reaction mixtures in which the presence of thiazoles of type **10** could only be detected in trace amounts. CuCl also promoted the formation of the corresponding thiazole derivatives **10**, albeit in 10–15% lower yields. Furthermore, the presence of an aromatic ring ad-

Table 2 MS, IR and NMR Data of Thiazoles **10a–d**

Product	MS *m/z* (%)	IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
10a	311 ($[M + 2]^+$, 8), 310 ($[M + 1]^+$, 25), 309 ($[M]^{+\cdot}$, 100), 281 (18), 280 (73), 264 (52), 237 (70), 134 (75), 133 (74), 105 (24), 89 (89)	2972, 1721, 1520, 1482, 1425, 1323, 1256, 1235, 1139, 1084, 1018, 758, 682, 604	1.34 (t, *J* = 7, 3 H), 4.35 (q, *J* = 7, 2 H), 7.5–7.55 (m, 6 H), 7.85–7.90 (m, 2 H), 8.05–8.1 (m, 2 H)	14.1 (q, CH_3), 61.5 (t, CH_2), 122.4 (s, C_{arom}), 126.9, 127.7, 129.0, 129.1, 129.9, 131.1, (d, CH_{arom}), 132.9, 134.2, 160.8, 161.6 (s, C_{arom}), 169.8 (s, CO)
10b	339 ($[M + 2]^+$, 8), 338 ($[M + 1]^+$, 25), 337 ($[M]^{+\cdot}$, 86), 336 (14), 309 (13), 308 (100), 292 (17), 290 (19), 265 (16), 264 (80), 218 (81), 190 (18), 160 (30), 128 (31), 116 (29), 145 (43), 104 (55), 91 (96)	3061, 3026, 2986, 2932, 1707, 1520, 1450, 1420, 1239, 1253, 1169, 1091, 764, 696	1.41 (t, *J* = 7.2, 3 H), 3.1–3.2 (m, 2 H), 3.5–3.6 (m, 2 H), 4.38 (q, *J* = 7.2, 2 H), 7.25–7.35 (m, 5 H), 7.5–7.55 (m, 3 H), 8.0–8.05 (m, 2 H)	14.3 (q, CH_3), 32.9, 35.4, 61.2 (t, CH_2), 125.9, 126.9, 128.3, 128.5, 129.0, 130.9 (d, CH_{arom}), 133.1, 141.5, 162.0, 164.2 (s, C_{arom}), 170.0 (s, CO)
10c	277 ($[M + 2]^+$, 4), 276 ($[M + 1]^+$, 11), 275 ($[M]^{+\cdot}$, 50), 260 (31), 248 (40), 247 (80), 246 (71), 232 (39), 230 (42), 218 (31), 202 (60), 176 (36), 175 (100), 121 (40), 104 (74), 97 (63)	2962, 2932, 2871, 1712, 1519, 1454, 1423, 1368, 1329, 1299, 1262, 1170, 1099, 1022, 765, 686	1.05–1.1 (m, 3 H, CH_3), 1.41 (t, *J* = 7.2, 3 H, CH_3), 1.75–1.95 (m, 2 H, CH_2), 3.15–3.25 (m, 2 H, CH_2), 4.38 (q, *J* = 7.2, 2 H), 7.45–7.55 (m, 3 H), 7.95–8.05 (m, 2 H)	14.0, 14.2 (q, CH_3), 22.7, 32.8, 61.1 (t, CH_2), 121.7 (s, C_{arom}), 126.8, 129.2, 130.8 (d, CH_{arom}), 133.0, 162.1, 165.4 (s, C_{arom}), 169.8 (s, CO)
10d	325 ($[M + 2]^+$, 12), 324 ($[M + 1]^+$, 40), 323 ($[M]^{+\cdot}$, 100), 295 (26), 294 (81), 278 (67), 252 (25), 251 (83), 250 (20), 145 (19), 135 (26), 134 (82), 133 (93), 119 (28), 90 (38), 89 (93)	3048, 2972, 2923, 1712, 1519, 1482, 1440, 1328, 1259, 1233, 1139, 1082, 1018, 817, 757, 699	1.34 (t, *J* = 7.2, 3 H), 2.45 (s, 3 H, CH_3), 4.33 (q, *J* = 7.2, 2 H), 7.25–7.30 (m, 2 H), 7.45–7.50 (m, 3 H), 7.85–8.00 (m, 4 H)	14.1, 21.5 (q, CH_3), 61.4 (t, CH_2), 121.9 (s, C_{arom}), 126.8, 127.7, 129.1, 129.7, 129.9 (d, CH_{arom}), 130.2, 134.3, 141.6, 161.0, 161.6 (s, C_{arom}), 170.0 (s, CO)



Scheme 4



Scheme 5

Table 3 2-Arylthiazoles **16a–h** Prepared

Product[a]	R	R^1	Yield (%)	Mp (°C)
16a	$PhCH_2CH_2$	Et	48	100–101
16b	Pr	Et	42	93–94
16c	$PhCH_2$	Et	42	141–142
16d	*i*-Pr	Et	47	95–96
16e	Me	Me	40	115–116
16f	Me	Me	41	101–102
16g	Chx[b]	Me	38	117–118
16h	*i*-Pr	Me	44	77–78

[a] Satisfactory microanalyses obtained: C ±0.27, H ±0.33, N ±0.25, S ± 0.29.
[b] Chx = cyclohexane.

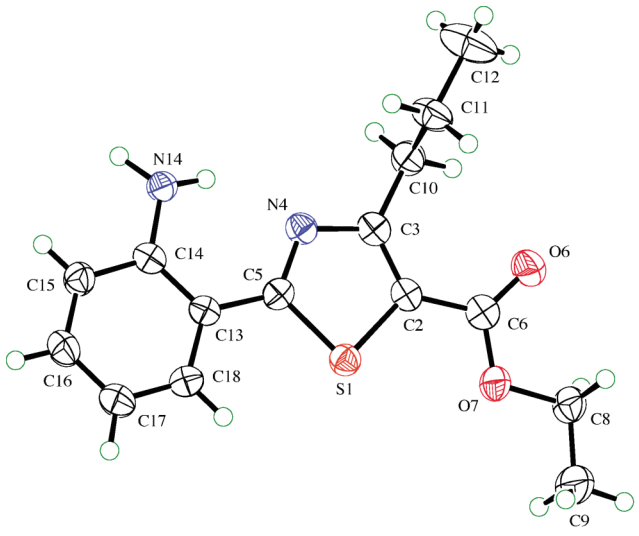


Figure ORTEP plot[42] of the molecular structure of **16b** with 50% probability ellipsoids

jacent to the thiocarbonyl group seemed to be essential in order to drive the reaction toward the formation of the corresponding thiazoles **10**. When aliphatic thioamides like thioacetamide or thiourea were subjected to analogous reaction conditions, the reaction did not result in the formation of any thiazoles. In these cases, we only could observe the decomposition of the diazo compounds **8** to give the parent β-keto esters **7**, plus the formation of stable Cu(I) complexes of the type $CuBr[RC(=S)NH_2]_4$, which were detected by cyclic voltammetric methods.[40,41]

With the aim of further extending the scope of the successful methodology developed herein toward the synthesis of 2-arylthiazoles **10**, we wished to use additionally functionalised aromatic thioamides that could further enhance the potential introduction of a higher degree of molecular diversity. For that purpose, we initially selected the anthranilic thioamide **14**, easily available in 72% from anthranilic amide **13** and Lawesson's reagent. This thioamide **14**, once transformed into the corresponding thiazole, would enable the introduction of additional diversity through suitable manipulations at the nitrogen atom of the aniline moiety. Thus, when a mixture of **14** and different α-diazo-β-keto esters of type **8** were prompted to react in the presence of 1 equivalent of CuBr in refluxing toluene, the corresponding thiazole derivatives **16a–h** were also obtained although in moderate yields (38–48%) (Scheme 5, Tables 3 and 4).

The presence of an additional nitrogen atom on the aromatic moiety could deactivate the copper catalyst to some extent through partial complexation, but the addition of additional amounts of CuBr did not improve the yields. The structural elucidation of the novel thiazole derivatives **16a–h** was accomplished by the usual spectroscopic methods, and in addition, **16b** was subjected to an X-ray crystal structure analysis, which unambiguously confirmed the structure (Figure).

Table 4 MS, IR and NMR Data of Thiazoles **16a–g**

Product	MS *m/z* (%)	IR (KBr) (cm^{-1})	^{1}H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
16a	354 ([M + 2]$^+$, 8), 353 ([M + 1]$^+$, 23), 352 ([M]$^{+\cdot}$, 100), 324 (18), 323 (79), 233 (42), 160 (11), 120 (10), 119 (22), 118 (23), 115 (18), 91 (60), 71 (14), 65 (25)	3431, 3316, 2956, 1690, 1618, 1477, 1412, 1278, 1103, 735	1.42 (t, *J* = 7.2, 3 H), 3.10–3.15 (m, 2 H), 3.45–3.6 (m, 2 H), 4.38 (q, *J* = 7.2, 2 H), 6.11 (br s, 2 H, NH_2), 6.7–6.8 (m, 2 H), 7.2–7.4 (m, 6 H), 7.6–7.65 (m, 1 H)	14.3 (q, CH_3), 32.4, 35.2, 61.1 (t, CH_2), 114.8 (s, C_{arom}), 116.8, 117 (d, CH_{arom}), 119.4 (s, C_{arom}), 125.9, 128.3, 128.4, 129.3, 131.7 (d, CH_{arom}), 141.3, 146.5, 162.1, 162.9 (s, C_{arom}), 171.5 (s, CO)
16b	292 ([M + 2]$^+$, 6), 291 ([M + 1]$^+$, 18), 290 ([M]$^{+\cdot}$, 100), 262 (45), 261 (26), 247 (10), 217 (10), 190 (71), 120 (10), 119 (31), 118 (51), 71 (20), 65 (14)	3359, 3233, 2954, 2868, 1708, 1619, 1524, 1262, 1103, 734	1.0–1.1 (m, 3 H), 1.4–1.45 (m, 3 H), 1.8–1.9 (m, 2 H), 3.15–3.2 (m, 2 H), 4.38 (q, *J* = 7, 2 H), 6.3 (br s, 2 H, NH_2), 6.7–6.8 (m, 2 H), 7.2–7.3 (m, 1 H), 7.6–7.7 (m, 1 H)	13.9, 14.3 (q, CH_3), 22.4, 32.7, 61.1 (t, CH_2), 114.9 (s, C_{arom}), 116.9, 117.1 (d, CH_{arom}), 119.1 (s, C_{arom}), 129.3, 131.7 (d, CH_{arom}), 146.5, 162.3, 164.1 (s, C_{arom}), 171.4 (s, CO)
16c	340 ([M + 2]$^+$, 6), 339 ([M + 1]$^+$, 23), 338 ([M]$^{+\cdot}$, 100), 309 (16), 292 (17), 266 (13), 265 (34), 148 (12), 147 (22), 146 (14), 136 (15), 118 (24), 103 (23), 102 (13), 91 (15)	3440, 3323, 2925, 1698, 1619, 1476, 1410, 1270, 1103, 1020, 728	1.43 (t, *J* = 7.2, 3 H), 4.41 (q, *J* = 7.2, 2 H), 4.57 (s, 2 H), 6.17 (br s, 2 H, NH_2), 6.7–6.75 (m, 2 H), 7.2–7.4 (m, 6 H), 7.6–7.65 (m, 1 H)	14.3 (q, CH_3), 36.6, 61.3 (t, CH_2), 114.7 (s, C_{arom}), 116.9, 117.1 (d, CH_{arom}), 119.6 (s, C_{arom}), 126.2, 128.4, 129.1, 129.2, 131.8 (d, CH_{arom}), 139.0, 146.6, 161.6, 162.2 (s, C_{arom}), 171.7 (s, CO)
16d	292 ([M + 2]$^+$, 4), 291 ([M + 1]$^+$, 19), 290 ([M]$^{+\cdot}$, 100), 262 (12), 261 (27), 247 (16), 143 (13), 119 (12), 118 (27), 99 (19), 98 (19)	3448, 3312, 2974, 2928, 1688, 1619, 1525, 1474, 1405, 1316, 1267, 1148, 1112, 790, 776	1.3–1.5 (m, 9 H), 4.05 (sept, *J* = 6.8, 1 H), 4.4 (m, q, *J* = 7.2, 2 H), 6.3 (br s, 2 H, NH_2), 6.7–6.8 (m, 2 H), 7.2–7.3 (m, 1 H), 7.65–7.7 (m, 1 H)	14.3, 22.1 (q, CH_3), 29.0 (d, CH), 61.1 (t, CH_2), 115.1 (s, C_{arom}), 117.0, 117.1 (d, CH_{arom}), 117.9 (s, C_{arom}), 129.3, 131.7 (d, CH_{arom}), 146.6, 162.2, 169.3 (s, C_{arom}), 171.6 (s, CO)
16e	264 ([M + 2]$^+$, 4), 263 ([M + 1]$^+$, 19), 262 ([M]$^{+\cdot}$, 100), 234 (47), 216 (14), 190 (12), 120 (62), 119 (22), 118 (97), 91 (19), 71 (27)	3477, 3442, 3303, 1692, 1614, 1490, 1473, 1373, 1330, 1296, 1104, 768	1.42 (t, *J* = 7.2, 3 H), 2.79 (s, 3 H), 4.38 (q, *J* = 7.2, 2 H), 6.21 (br s, 2 H, NH_2), 6.7–6.8 (m, 2 H), 7.2–7.25 (m, 1 H), 7.65–7.7 (m, 1 H)	14.3, 17.5 (q, CH_3), 61.1 (t, CH_2), 114.7 (s, C_{arom}), 116.8, 117.0 (d, CH_{arom}), 119.1 (s, C_{arom}), 129.2, 131.6 (d, CH_{arom}), 146.5, 159.8, 162.3 (s, C_{arom}), 171.3 (s, CO)
16f	250 ([M + 2]$^+$, 17), 249 ([M + 1]$^+$, 73), 248 ([M]$^{+\cdot}$, 66), 154 (100), 152 (10), 149 (17), 139 (16), 138 (36), 137 (71), 136 (87)	3430, 3295, 2952, 2926, 1685, 1618, 1618, 1600, 1475, 1416, 1334, 1283, 1104, 738	2.80 (s, 3 H, CH_3), 3.93 (s, 3 H, CH_3), 6.26 (br s, 2 H, NH_2), 6.7–6.8 (m, 2 H), 7.2–7.3 (m, 1 H), 7.6–7.65 (m, 1 H)	17.5, 52.1 (q, CH_3), 114.6 (s, C_{arom}), 117.0, 117.1 (d, CH_{arom}), 118.6 (s, C_{arom}), 129.3, 131.8 (d, CH_{arom}), 146.5, 160.2, 162.8 (s, C_{arom}), 174.3 (s, CO)
16g	318 ([M + 2]$^+$, 22), 317 ([M + 1]$^+$, 100), 316 ([M]$^{+\cdot}$, 26), 315 (13), 261 (11), 149 (57), 109 (96)	3366, 3260, 2922, 2846, 1717, 1619, 1509, 1410, 1302, 1264, 1251, 1094, 734	1.25–1.95 (m, 10 H), 3.65–3.75 (m, 1 H), 3.91 (s, 3 H, CH_3), 6.27 (br s, 2 H, NH_2), 6.7–6.8 (m, 2 H), 7.2–7.25 (m, 1 H), 7.6–7.65 (m, 1 H)	26.0, 26.41, 32.4 (t, CH_2), 39.0 (d, CH), 52.0 (q, CH_3), 115.0 (s, C_{arom}), 117.0, 117.1 (d, CH_{arom}), 117.3 (s, C_{arom}), 129.2, 131.7 (d, CH_{arom}), 146.5, 162.5, 169.0 (s, C_{arom}), 171.6 (s, CO)
16h	278 ([M + 2]$^+$, 12), 277 ([M + 1]$^+$, 35), 276 ([M]$^{+\cdot}$, 100), 262 (18), 261 (77)	3432, 3307, 3210, 2969, 2932, 2870, 1688, 1619, 1559, 1514, 1482, 1436, 1413, 1336, 1317, 1284, 1230, 1190, 1092, 1031, 763, 740	1.37 (d, *J* = 3.5, 6 H), 3.9 (s, 3 H), 4.0–4.1 (m, 1 H), 5.88 (br s, 2 H), 6.7–6.8 (m, 2 H), 7.2–7.3 (m, 1 H), 7.6–7.65 (m, 1 H)	22.1 (q, CH_3), 28.9 (d, CH), 52.0 (q, CH_3), 115.1, 117.1 (s, C_{arom}), 117.2, 129.2, 131.6 (d, CH_{arom}), 145.9 (s, C_{arom}), 146.0 (d, CH_{arom}), 162.4, 169.5 (s, C_{arom}), 171.6 (s, C=O)

Table 5 2-Arylthiazoles 17a,b and 18a,b Prepared

Product[a]	R	Yield (%)	Mp (°C)
17a	Chx	69	152–153
17b	*i*-Pr	70	139–140
18a	Chx	94	228–229
18b	*i*-Pr	93	237–238

[a] Satisfactory microanalyses obtained: C ± 0.34, H ± 0.29, N ± 0.28, S ± 0.31.

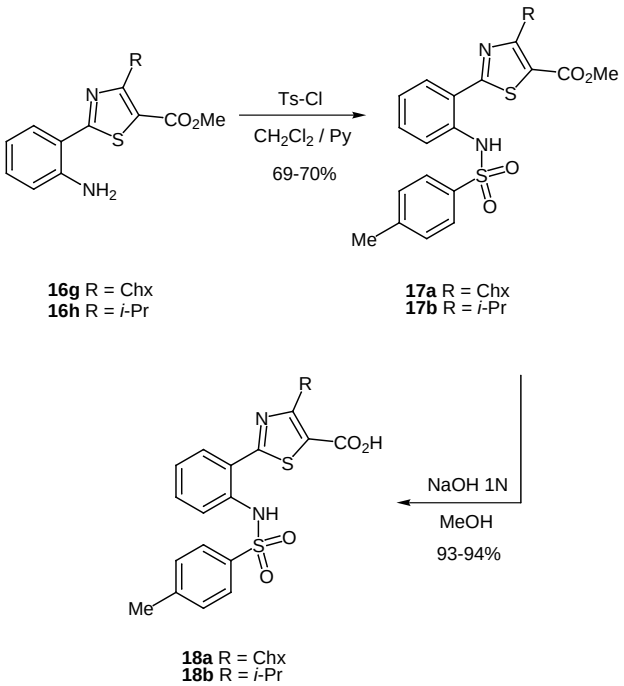
Finally, and just to show that our initial working hypothesis regarding the introduction of further diversity through the aniline moiety was feasible, compounds **16g** and **16h** were sulfonylated with TsCl in CH_2Cl_2–pyridine to give **17a,b** in high yields. Saponification of the ester moiety with 1 N NaOH/MeOH afforded the corresponding carboxylic acids **18a,b**, also in good yields (Scheme 6, Tables 5 and 6).

In summary, we have developed a simple methodology that allows novel trisubstituted thiazoles **10** and **16** to be

Table 6 MS, IR and NMR Data of Thiazoles **17a,b** and **18a,b**

Product	MS *m/z* (%)	IR (KBr) (cm^{-1})	^1H NMR ($CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ
17a	472 ($[M + 2]^+$, 4), 471 ($[M + 1]^+$, 9), 470 ($[M]^+$, 30), 415 (5), 402 (6), 316 (20), 315 (100), 283 (20), 260 (20), 255 (12), 247 (15), 227 (6), 217 (5)	2927, 2849, 1718, 1512, 1438, 1344, 1263, 1161, 1093, 913, 812, 758, 662	1.45–1.95 (m, 10 H), 2.35 (s, 3 H), 3.65–3.75 (m, 1 H), 3.94 (s, 3 H), 7.05–7.80 (m, 8 H)	20.5 (q, CH_3), 24.9, 25.5, 31.5 (t, CH_2), 38.1 (d, CH), 51.3 (q, CH_3), 118.4, 118.6 (s, C_{arom}), 119.0, 122.5, 126.0, 127.8, 128.5, 130.9 (d, CH_{arom}), 135.5, 136.0, 142.6, 161.0, 167.5 (s, C_{arom}), 169.0 (s, CO)
17b	432 ($[M + 2]^+$, 9), 431 ($[M+1]^+$, 17), 430 ($[M]^+$, 70), 366 (27), 276 (28), 275 (100), 260 (18), 243 (68), 215 (34), 91 (73), 65 (31)	2972, 2928, 2869, 1715, 1461, 1343, 1319, 1254, 1162, 1093, 920, 764, 663	1.46 (d, *J* = 6.8, 6 H), 2.35 (s, 3 H), 3.94 (s, 3 H), 4.00–4.10 (m, 1 H), 7.05–7.20 (m, 3 H), 7.35–7.40 (m, 1 H), 7.65–7.80 (m, 4 H)	21.4, 22.2 (q, CH_3), 29.0 (d, CH), 52.3 (q, CH_3), 119.3, 119.4 (s, C_{arom}), 119.7, 123.4, 127.0, 128.8, 129.5, 131.9 (d, CH_{arom}), 136.5, 137.0, 143.6, 161.9, 169.0 (s, C_{arom}), 170.1 (s, CO)
18a	414 ($[M - CO_2 + 2]^+$, 3), 413 ($[M - CO_2 + 1]^+$, 6), 412 ($[M - CO_2]^+$, 22), 348 (3), 258 (19), 257 (100), 202 (10), 189 (11), 136 (5), 119 (6), 118 (5), 97 (8), 91 (21)	2926, 2852, 1706, 1633, 1520, 1345, 1302, 1263, 1161, 1093, 919, 755, 668	1.30–2.05 (m, 10 H), 2.39 (s, 3 H), 3.70–3.80 (m, 1 H), 7.25–7.40 (m, 3 H), 7.50–7.70 (m, 4 H), 7.90–7.95 (m, 1 H), 12.16 (s, 1 H)[a]	20.9 (q, CH_3), 25.6, 26.0, 32.0 (t, CH_2), 35.7 (d, CH), 120.1, (s, C_{arom}), 120.2 (d, CH_{arom}), 121.8, (s, C_{arom}), 124.6, 126.6, 129.3, 129.8, 132.1 (d, CH_{arom}), 135.7, 135.8, 144.0, 162.3, 166.0 (s, C_{arom}), 168.3 (s, CO)[a]
18b	374 ($[M - CO_2 + 2]^+$, 4), 373 ($[M - CO_2 + 1]^+$, 8), 372 ($[M - CO_2]^+$, 37), 308 (11), 218 (15), 217 (100), 202 (17), 201 (10), 149 (5), 91 (16), 85 (7)	2979, 2940, 2877, 1670, 1517, 1412, 1320, 1270, 1159, 907, 760	1.37 (d, *J* = 6.8, 6 H), 2.30 (s, 3 H), 3.95–4.05 (m, 1 H), 7.15–7.85 (m, 8 H)	20.9, 22.0 (q, CH_3), 28.1 (d, CH), 119.8 (s, C_{arom}), 119.9 (d, CH_{arom}), 121.6 (s, C_{arom}), 124.5, 126.6, 129.3, 129.9, 132.1 (d, CH_{arom}), 135.7, 135.8, 144.0, 162.3 (s, C_{arom}), 166.8 (s, CO), 168.5 (s, C_{arom})

[a] NMR spectra were recorded in DMSO-d_6.



Scheme 6

synthesized from easily available starting materials. The method is based on the key role played by Cu(I) which presumably catalyses the formation of intermediates **12** from carbenoids **11** and leads to the corresponding thiazole derivatives **10** and **16**. The easy access to the corresponding starting materials **8**, **9** and **14** permits the potential introduction of a wide range of structural variations and therefore makes this method an attractive alternative route for the synthesis of novel thiazole derivatives with a high degree of molecular diversity. The limitation imposed by the fact that only aromatic thioamides can undergo this type of transformation (no restrictions were found within the diazo carbonyl ester derivatives) should be considered as a disadvantage. Nevertheless, due to the importance of the thiazole nucleus in medicinal chemistry (the thiazole ring is a pharmacophore widely distributed in many biologically active molecules[43–46]), the development of new synthetic repertoires for the preparation of novel members of this important class of heterocycles is of current interest.

All commercially available chemicals were used as purchased. CH_2Cl_2 was dried over CaH_2 and kept over activated molecular sieves (4Å). Toluene and THF were dried over Na/benzophenone prior to use. All reactions were run under a positive pressure of dry N_2. Melting points (capillary tube) were measured with an electrothermal digital melting point apparatus, IA 9100 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Brucker DPX200 Advance instrument with TMS as the internal standard. MS spectra were recorded on a VG Quattro instrument in the positive ionisation FAB mode, using 3-NBA or 1-thioglycerol as the matrix. Elemental analyses were performed on an apparatus from Thermo instruments, model EA1110-

CHNS. Analytical TLC was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). Flash-chromatography purifications were performed on silica gel 60 (230–400 mesh, Merck).

Thioamide 9b

To a solution of 4-Methylbenzonitrile (2.9 g, 25 mmol) in a mixture of absolute EtOH (13 mL) and 25% aq NaOH (2 mL) was added 35% H_2O_2 (10 mL). The mixture was stirred at r.t. for 0.5 h. Additional 25% aq NaOH (2 mL) and 35% H_2O_2 (5 mL) were added and the mixture stirred at r.t. for 2 h. Then 50% H_2SO_4, was added until pH 3–4. EtOH was distilled off, and the resulting residue was partitioned between H_2O (10 mL) and EtOAc (30 mL). To the aqueous layer, aq 25% NaOH was added until pH 7–8 and extracted with EtOAc (30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give the corresponding 4-methylbenzamide as a colourless solid (3.34 g, 99%), pure enough to be used in the next step; mp 158–159 °C.

IR (KBr): 3342, 3164, 1670, 1616, 1567, 1412, 1386, 1178, 1144, 1119, 840, 792, 728, 670, 629, 587, 528, 456 cm^{-1}.

MS: *m*/*z* (%) = 136 ($[M + 1]^+$, 10), 135 ($[M]^{+\cdot}$, 90), 119 (100), 92 (12), 91 (90), 90 (10), 89 (21), 65 (45), 63 (16).

To a solution of the above 4-methylbenzamide (1 g, 7.4 mmol) in THF (30 mL) was added the Lawesson's reagent (1.64 g. 4.1 mmol). The mixture was stirred under N_2 at r.t. for 24 h. The solvent was evaporated, and the residue partitioned between $CHCl_3$ (30 mL), and aq 10% $NaHCO_3$ (30 mL). The organic layer was separated, dried ($MgSO_4$) and filtered. The solvent was evaporated and the resulting solid residue recrystallised from MeCN to afford pure **9b** as a yellow solid; yield: 0.81 g (72%); mp 166–167 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.64 (br s, 2 H, NH_2), 2.43 (s, 3 H, CH_3), 7.2–7.3 (m, 2 H_{arom}), 7.8–7.85 (m, 2 H_{arom})

IR (KBr): 3376, 3276, 3157, 1622, 1413, 1321, 1270, 1181, 1132, 879, 821, 791, 711, 595, 475 cm^{-1}.

MS: *m*/*z* (%) = 153 ($[M + 2]^+$, 8), 152 ($[M + 1]^+$, 18), 151 ($[M]^{+\cdot}$, 83), 117 (100), 116 (65), 90 (47).

2-Aminothiobenzamide (14)

To a solution of **13** (2 g, 14.7 mmol) in THF (73 mL) was added the Lawesson's reagent (3.23 g. 8 mmol). The mixture was stirred under N_2 at r.t. for 24 h. The solvent was evaporated, and the residue partitioned between EtOAc (50 mL), and 1 N HCl (30 mL). To the aqueous layer was added aq sat. $NaHCO_3$ until pH 8–9. The basic solution extracted with EtOAc (2 × 30 mL). The combined organic layers were dried ($MgSO_4$) and filtered. The solvent was evaporated and the resulting solid residue recrystallised from toluene to afford pure [14] as a yellow solid; yield: 1.62 g (72%); mp 116–117 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.47 (br s, 2 H, NH_2), 6.7–6.8 (m, 2 H_{arom}), 7.2–7.4 (m, 2 H_{arom} + NH_2).

^{13}C NMR (50 MHz, DMSO–d_6): δ = 115.2, 116.2, (d, CH_{arom}), 123.7 (s, C_{arom}), 127.0, 130.8 (d, CH_{arom}), 147.2 (s, C_{arom}), 200.2 (s, C=S).

IR (KBr): 3409, 3286, 3070, 1650, 1604, 1582, 1489, 1454, 1410, 1328, 1287, 908, 754 cm^{-1}.

MS: *m*/*z* (%) = 152 ($[M]^{+\cdot}$, 83), 119 (100), 118 (60), 92 (41), 91 (35), 65 (40), 64 (21).

2-Arylthiazoles 10a–d and 16a–h; General Procedure

A mixture containing the corresponding aromatic thioamides **9a–b** or **14** (1 mmol), each of the different diazo derivatives **8** (1 mmol) and CuBr (1 mmol) in anhyd toluene (5 mL) was stirred under N_2 at reflux temperature for 2 h. The suspension was filtered through a fluted filter paper, and washed with toluene. The solvent was evaporated and the residue purified by flash-chromatography (hexane–EtOAc) to afford pure **10a–d** and **16a–h** (Tables 1– 4).

Crystal Data for Compound 16b[47]

$C_{15}H_{18}N_2O_2S$, M_r = 290.38, monoclinic, space group *C*2/*c*, *a* = 27.880(3), *b* = 4.864(4), *c* = 23.585(2) Å, β = 109.614(8)°, *V* = 3013(2) Å^3, *Z* = 8, D_c = 1.280 g cm^{-3}, crystal dimensions: 0.17 × 0.22 × 0.48 mm, *T* = –100 °C, Rigaku AFC5R diffractometer, Mo *K*α radiation, λ = 0.71069 Å, μ = 0.218 mm–1, ω–2θ scans, $2\theta_{max}$ = 55°, 3959 measured reflections of which 3471 were unique. The intensities were corrected for *Lorentz* and polarization effects. An empirical absorption correction based on ψ-scans[48] was applied. The structure was solved by direct methods using SIR92[49] and refined on *F* by full-matrix least-squares methods using teXsan.[50] The positions of the amine H-atoms were refined isotropically, while all other H-atoms were in calculated positions. The refinement of 189 parameters using 2161 observed reflections with $I > 2\sigma(I)$ gave R1 = 0.0501, *w*R2 = 0.0426, S = 1.792, and $\Delta\rho_{max}$ = 0.28 e Å^{-3}.

Tosyl Thiazole Derivatives 17a,b; General Procedure

To a solution of **16g**,**h** (0.39 mmol) in anhyd CH_2Cl_2 (2 mL) was added pyridine (0.03 mL, 0.39 mmol) and a solution of *p*-toluenesulfonyl chloride (0.077g, 0.39 mmol) in anhyd CH_2Cl_2 (2 mL). The mixture was stirred at r.t. for 48 h, then diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (3 × 20 mL). The separated organic layer was dried ($MgSO_4$), filtered and concentrated. The resulting crude material was purified by flash column chromatography (hexane–EtOAc, 10:1 as eluent) (Tables 5 and 6).

Thiazole Carboxylic Acid Derivatives 18a,b; General Procedure

To a solution of **17a**,**b** (0.5 mmol) in MeOH (1 mL) was added aq 1 N NaOH (1 mL). The mixture was stirred at r.t. for 24 h. 1 N HCl was added until pH 3 was reached and then extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated under reduced pressure to afford pure **18a**,**b** as colourless solids (Tables 5 and 6).

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