Facile Generation of a Library of 5-Aryl-2-arylsulfonyl-1,3-thiazoles

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Abstract: Treatment of *N*,*N*-diformylaminomethyl aryl ketones with phosphorus pentasulfide/triethylamine in chloroform gives 5-arylthiazoles directly in good yield. The 5-aryl-1,3-thiazole core has been successfully functionalised at the 2-position to yield, over two steps, a large array of 5-aryl-2-arylsulfonyl-1,3-thiazoles in a parallel fashion.

Key words: heterocycles, 1,3-thiazole, lithiation, phosphorus pentasulfide

The preparation of 4-aryl-1,3-thiazoles by the classical Hantzsch synthesis of α-bromoacetophenones with thioformamide is one of the most widely used and reliable reactions in heterocyclic synthesis.[1] In contrast, the preparation of the regioisomeric 5-arylthiazoles is problematic as either α-aminoacetophenones or α-halo-α-arylacetaldehydes are required, neither of which is an easily handled intermediate. Consequently, reactions have been devised to attach an aryl group at the thiazole 5-position. Palladium(0) and aryl bromides/iodides are used with 5-unsubstituted thiazoles[2–5] and a cobalt catalyst has been similarly employed.[6] A 5-chlorothiazole has been used for Suzuki coupling.[7] When the thiazole 2-position is blocked, deprotonation at the 5-position with *n*-butyllithium, transmetallation and Negishi cross-coupling has been exemplified.[8]

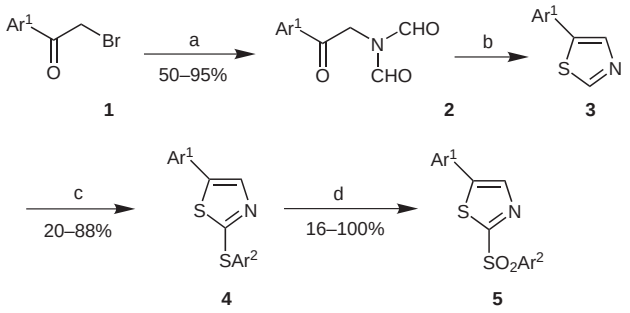
Within a project, we needed a range of 5-arylthiazoles for conversion to 2-substituted-5-arylthiazoles. We thought that such thiazoles should be prepared by thiazole ring formation. The reaction of sodium diformylamide and α-bromoketones to produce *N*,*N*-diformylaminoketones such as **2** is reported,[9] but surprisingly we found no mention of these compounds being used directly for the preparation of heterocycles. In contrast, the monoformylaminoketones have been converted to thiazoles using phosphorus pentasulfide.[10]

We reasoned that it might be unnecessary to remove a formyl group from **2** in a separate step as this would likely happen during or as a result of the cyclisation step. We prepared bromomethylketones **1** either by Friedel–Crafts reaction of the aromatic with bromoacetyl bromide or by bromination of the methyl ketone, and displaced the bromine using sodium diformylamide.[9] Reaction of 2-diformylamino-1-phenylethanone with 1.2 equivalents of Lawesson's reagent in toluene gave a low yield of 5-phenyl-1,3-thiazole (Table 1).

Table 1 Conditions for the Preparation of 5-Phenyl-1,3-thiazole

Reagent (equiv)	Et_3N (equiv)	Solvent	Temp (°C)	Time (min)	Yield (%)
Lawesson's (1.2)	–	PhMe	90	70	14
Lawesson's (2.2)	–	PhMe	90	110	37
Lawesson's (2.0)	2	PhMe	90	90	55
P_2S_5 (2.0)	2	PhMe	90	120	62
P_2S_5 (2.2)	2.2	$CHCl_3$	60	45	82

Increasing the amount of reagent and adding triethylamine improved the yield, but impurities derived from the Lawesson's reagent were difficult to remove from the product. Using phosphorus pentasulfide and changing the solvent to chloroform brought further enhancement of the yield.[11,12] We did not observe any intermediate, which would have helped us ascertain whether a formyl group is lost before or after thiazole formation. Yields of other 5-arylthiazoles **3**[13,14] are shown in Table 2.



Scheme 1 *Reagents and conditions*: (a) $NaN(CHO)_2$, MeCN, 70 °C; (b) P_2S_5, Et_3N, $CHCl_3$, 60 °C, 45–60 min; (c) (i) LDA (1.3 equiv), THF, –70 °C, 50 min, (ii) Ar^2SSAr^2 (1.3 equiv), –70 °C to r.t., 45 min; (d) (i) MCPBA (5 or 10 equiv), CH_2Cl_2, r.t. or 40 °C, 3 h or 6 h, (ii) MP-carbonate resin (4 peracid equiv), CH_2Cl_2, 2 h, r.t.

As anticipated, we were able to functionalise the 2-position of the thiazole by deprotonation with a modest excess of LDA, followed by reaction with an electrophile. With diaryldisulfides, we obtained thioethers **4** in yields of, typically, greater than 70%.[15,16] Surprisingly, we find little precedent for the use of disulfides with 2-lithiothiazoles and these examples used only dimethyldisulfide.[17,18] The thioethers were easily oxidised to the corresponding

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Table 2 Yields of 5-Aryl-1,3-thiazoles **3** Prepared via Scheme 1.

Ar^1	Yield (%)
4-FC_6H_4	79
2-$MeOC_6H_4$	54
4-$MeOC_6H_4$	78
2-MeC_6H_4	79
4-MeC_6H_4	83
3-$NO_2C_6H_4$	47
4-ClC_6H_4	76
1-Naphthyl	63
2-Naphthyl	69
2-Furyl	75
2-Thienyl	61

sulfones **5**, which were obtained in pure form by simple treatment of the crude mixtures with MP-carbonate resin[19] and subsequent filtration, with no need for aqueous work up.[20–23] We found the chemistry described here convenient to carry out using a parallel reactor and we were able to obtain a large array of compounds for project purposes in a short time.

In summary, a convenient preparation of 2,5-substituted-1,3-thiazoles has been reported. This synthetic procedure is amenable for parallel synthesis applications allowing the rapid preparation of large arrays of compounds in a short time from easily available starting materials and reagents.

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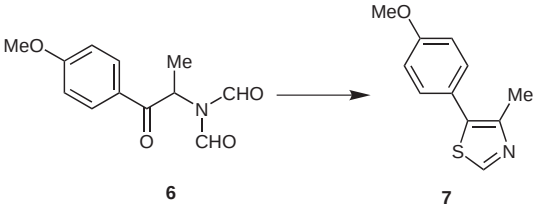
(11) **General Procedure for the Preparation of Thiazoles 3.** The bisformamide derivative (1 mmol) was dissolved in $CHCl_3$ (5 mL). Then, Et_3N (0.28 mL, 0.20 g, 2 equiv) was added to the stirred mixture, followed by phosphorus pentasulfide (0.44 g, 2 mmol, 2 equiv). The mixture was stirred at 60 °C for the appropriate time (typically 45–60 min). After cooling to r.t., H_2O (3 mL) was added and the mixture stirred for 1 h. CH_2Cl_2 (15 mL) was then added and layers separated. The organic layer was washed with H_2O and brine, dried (Na_2SO_4 or $MgSO_4$) and the solvent removed in vacuo. The crude product was purified by flash chromatography [silica; Et_2O–PE (60–80) mixtures as eluant] or on silica preparative TLC plates.
(12) We were also able to convert **6** into the thiazole **7** by the same method in 67% yield (Scheme 2).



6 **7**

Scheme 2

(13) Spectroscopic data of **3** (Ar^1 = 4-$MeOC_6H_4$): ^1H NMR (250 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 7.50 (m, 2 H), 6.94 (m, 2 H), 7.98 (s, 1 H), 8.70 (s, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 55.53, 114.7, 123.8, 128.4, 138.2, 139.4, 151.4, 160.0.
(14) Spectroscopic data of **3** (Ar^1 = 2-furyl): ^1H NMR (250 MHz, $CDCl_3$): δ = 6.46 (dd, *J* = 3.5, 1.8 Hz, 1 H), 6.57 (dd, *J* = 3.5, 0.6 Hz, 1 H), 7.45 (dd, *J* = 1.8, 0.6 Hz, 1 H), 8.05 (s, 1 H), 8.71 (s, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 107.6, 111.94, 129.2, 138.7, 142.8, 146.4, 151.4.
(15) Spectroscopic data of **4** (Ar^1 = 3-$NO_2C_6H_4$, Ar^2 = 3-BrC_6H_4): ^1H NMR (250 MHz, $CDCl_3$): δ = 7.33 (m, 1 H), 7.52–7.68 (m, 3 H), 7.72–7.87 (m, 2 H), 7.97 (s, 1 H), 8.12–8.22 (m, 1 H), 8.28 (m, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 121.3, 123.0, 123.6, 130.32, 130.36, 131.3, 132.3, 132.7, 133.1, 133.4, 136.3, 138.4, 140.4, 148.85, 148.86.
(16) Spectroscopic data of **4** (Ar^1 = 4-MeC_6H_4, Ar^2 = Ph): ^1H NMR (250 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 7.11–7.23 (m, 2 H), 7.29–7.51 (m, 5 H), 7.65 (m, 2 H), 7.82 (s, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.3, 126.5, 128.2, 129.5, 129.8, 132.2, 133.6, 138.3, 138.5, 141.2, 164.2.
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(19) MP-carbonate resin (loading: 3.14 mmol/g) was purchased from Argonaut Technologies.
(20) **General Procedure for the Oxidation of Thioethers 4 to Sulfones 5**. To a solution of the thioether (1 equiv, 0.2 M) in CH_2Cl_2, dry MCPBA (5 or 10 equiv) was added. The resulting mixture was stirred for 3 h at 40 °C (recommended for sterically hindered thioethers) or 6 h at r.t. To the mixture diluted with CH_2Cl_2 (35 mL/mmol of thioether), MP-carbonate resin was added (4 equiv relative to the amount of peracid used) and stirred for 2 h. The resin was filtered off and washed twice

with CH_2Cl_2. The solvent was removed in vacuo to give the expected sulfones in pure form. In a few cases, crude sulfones required further purification by preparative TLC (silica; Et_2O–PE (60–80) 7:3 as eluant).

(21) Sulfones derived from 5-furylsubstituted thiazoles could not be isolated, probably due to side reactions affecting the furan ring under the acidic conditions used for the oxidation step.

(22) Spectroscopic data of **5** (Ar^1 = 4-$MeOC_6H_4$, Ar^2 = 4-MeC_6H_4): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.84 (s, 3 H), 6.89–7.01 (m, 2 H), 7.31–7.42 (m, 2 H), 7.43–7.53 (m, 2 H), 7.91–8.10 (m, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 21.8, 55.6, 115.0, 122.2, 128.7, 130.2, 136.2, 139.5, 145.6, 146.9, 161.0, 164.2.

(23) Spectroscopic data of **5** (Ar^1 = 2-thienyl, Ar^2 = 2-MeC_6H_4): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.65 (s, 3 H), 7.01 (dd, *J* = 5.0, 3.7 Hz, 1 H), 7.18–7.52 (m, 5 H), 7.84 (s, 1 H), 8.16 (m, 1 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 20.9, 127.0, 127.7, 127.9, 128.6, 130.6, 131.1, 133.1, 134.7, 137.2, 139.6, 139.9, 140.2, 164.7.