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A practical preparation of 5-(ketoaryl)thiazoles

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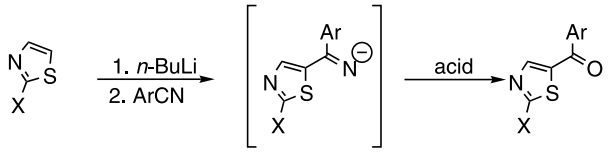
Abstract—This article describes a facile synthesis of 2-substituted-5-(ketoaryl)thiazoles, which are important intermediates for the synthesis of biologically active compounds. A variety of 2-substituted thiazole anions were added to aryl nitriles to provide the desired ketones after aqueous hydrolysis.

Thiazoles are important heterocycles in pharmaceutical organic chemistry and are often used as amide isosteres during the course of probing structure activity relationships. In light of this, a useful intermediate for the construction of biaryl thiazoles is the 5-(ketoaryl)thiazole. These thiazoles are classically assembled using the Hantzsch reaction,[1] i.e. condensation of a thiourea with an amide acetal to form a thiocarbamoylamidine, followed by base-promoted cyclization with a phenacyl halide. While the thiourea and formamide can be appended with alkyl groups to produce diversely substituted thiazoles, this method is limited in that it only produces thiazoles with an alkylamino group in the 2-position.[2]

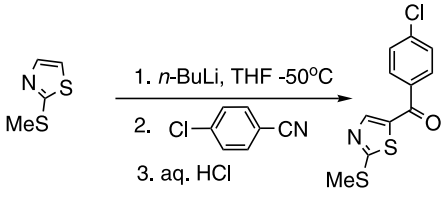
The synthesis of 5-(ketoaryl)thiazoles lacking an amine in the 2-position involves deprotonation of 2-substituted thiazoles in the 5-position, followed by addition to acid chlorides,[3a] amides,[3b] ketenes,[3a] lactones,[3c] and aldehydes[3d] (with subsequent oxidation) to afford the desired ketone. However, these functional groups often require synthetic manipulation to obtain and the reaction intermediates may not be stable to some reaction conditions. An appealing alternative would be addition of the thiazole anion to a nitrile functionality,[4] followed by hydrolysis of the intermediate metallo imine species to the ketone (Scheme 1). This would constitute a convenient synthesis of 5-(ketoaryl)thiazoles, as many substituted benzonitriles and 2-substituted thiazoles are readily available, and the nitrile functionality is stable to a range of reaction conditions. Furthermore, unlike reactions with functional groups that are susceptible to overaddition, the imine intermediate is unlikely to react with a second thiazole anion.



Scheme 1. Thiazole anion addition to nitriles.

The reaction conditions were developed as follows. Treatment of a low temperature THF solution of the thiazole with *n*-BuLi effected clean deprotonation at the 5-position, as demonstrated by deuterium quenching experiments. Subsequent addition of the nitrile followed by aging between −35 and −20°C resulted in complete conversion to the lithio imine intermediate.[5] After acidic hydrolysis, the ketones were obtained in good to excellent yields.

Scheme 2 illustrates one example (entry 1, Table 1): 4-Chlorobenzonitrile was added to lithiated 2-(methylthio)thiazole, and the reaction was aged for 2 h to give 90% HPLC assay yield of the ketone, after an aq. HCl work-up to hydrolyze the imine.[6,7]



Scheme 2. Example of thiazole addition chemistry.

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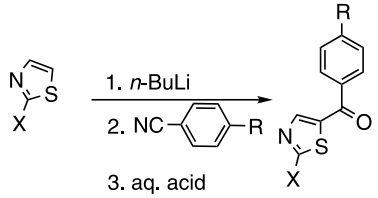
In order to demonstrate this as a general method, a range of thiazoles were added to commercially available nitriles. Inspection of Table 1 reveals that the reaction was tolerant of electron withdrawing and donating groups on both reacting partners.

Table 1. Effect of substitution on thiazole and benzonitrile



Entry	X	R	Rxn time (h)	Yield (%)[a]
1	SMe[b]	Cl	2	90
2	SMe	H	3	90
3	SMe	OMe	4	94
4	Si*t*BuMe$_2$[c]	Cl	1.5	98
5	Si*t*BuMe$_2$	H	1.5	98
6	Si*t*BuMe$_2$	OMe	8	88[e]
7	C(CF$_3$)$_2$OMOM[d]	H	3	95
8	C(CF$_3$)$_2$OMOM	OMe	5	96

[a] Assay yields determined by HPLC, compared with a standard.
[b] Prepared from 2-mercaptothiazole and MeI with K_2CO_3 in MeCN.
[c] Prepared from thiazole and TBSCl using *n*-BuLi.
[d] Prepared by deprotonating thiazole with LiHMDS, quenching with hexafluoroacetone, followed by addition of MOMCl.
[e] Yield of X = H, TBS was removed in work-up.

It is important to note that temperature control was crucial in this reaction due to competitive decomposition of the iminium intermediate. Decomposition generally occurred at temperatures above −10°C, while the addition reactions were sluggish at −50°C. As a result, reactions were typically run between −35 and −20°C to effect complete conversion within a few hours, while minimizing decomposition.

The stability of the intermediate imine was notable. The electronic parameters of the reacting partners had an effect on the stability, and several of these imines could be isolated and characterized. To isolate the imine, the reaction was quenched into aq. NH_4Cl, while aq. AcOH or 2N HCl was used to effect hydrolysis to the ketone. Electron poor imines generally hydrolyzed instantly in acid, while electron rich imines required a longer age to hydrolyze completely.[8]

The TBS group on the thiazole proved to be a versatile appendage. It was discovered during hydrolysis of the imine that an overnight age in aq. AcOH retained the TBS group on the ketone product while an HCl quench removed it completely.[9] This lability of the TBS group could be exploited as a temporary protecting group for the 2-position to obtain ketones capable of being further functionalized at that position. Notably, when the commercially available 2-(trimethylsilyl)thiazole was used, products were detected that arose from reaction at the 2-position, indicating that the TMS functionality was somewhat labile under reaction conditions. This was not an issue with the more robust TBS group.

To probe the utility of this reaction further, 2-(*t*-butyldimethylsilyl)thiazole was deprotonated and added to a variety of electronically and structurally different aryl nitriles (Table 2). The reaction was found to be tolerant of substituents *ortho* to the nitrile, although in a comparative study, reaction was significantly slower with the more hindered 2-methyl- versus 4-methylbenzonitrile (entries 1 and 2, Table 2). However, when a bulky EWG was *ortho* to the nitrile, the rate appeared unaffected, suggesting that ring electronics may have a significant effect on the rate of reaction (entry 3, Table 2). In line with these findings, when an OMe was in the *meta* position of the benzonitrile ring (entry 4, Table 2), the rate of reaction was faster than when the same group was in the *para* position (entry 6, Table 1).

To expand the scope of this reaction, other aryl nitriles and substituted thiazoles were investigated. Extension of this method into heteroaromatic nitriles would lead to products of even greater structural diversity, and it was found that 5-lithio-2-substituted thiazoles added to 4-cyanopyridine and 2-furonitrile to form biheteroaryl ketones in good and moderate yields, respectively (entries 7–9, Table 2). In a similar vein, thiazoles containing a masked ketone and a masked amine (entries 10 and 11, Table 2) were prepared and found to provide high yields of 5-(ketoaryl)thiazoles capable of further functionalization.

In conclusion, a facile method for the preparation of 5-(ketoaryl)thiazoles from 2-substituted thiazoles and aryl nitriles has been developed. This method is applicable to a broad range of substituted aryl and heteroaryl nitriles as well as functionalized thiazoles and affords the ketones in good to excellent yields. These ketone intermediates can provide a base on which to create pharmaceutically interesting compounds.

Acknowledgements

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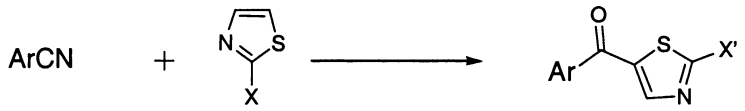
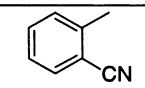
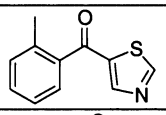
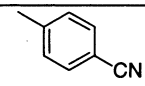
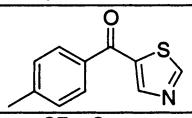
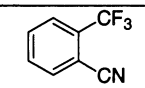
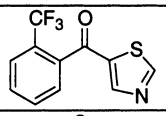
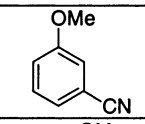
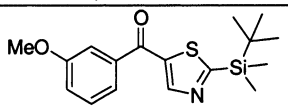
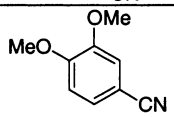
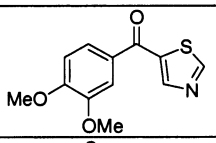
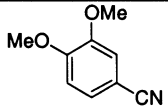
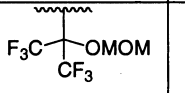
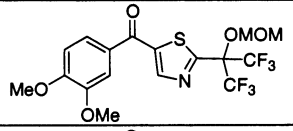
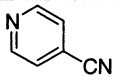
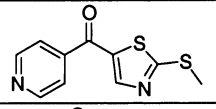
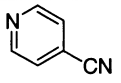
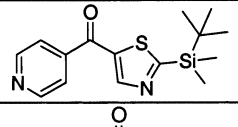
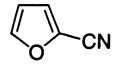
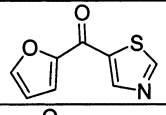
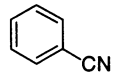
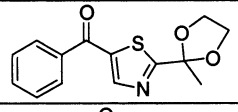
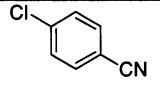
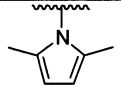
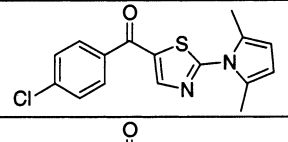
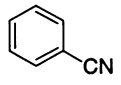
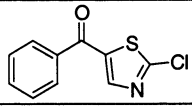
Table 2. Addition of 2-substituted thiazoles to a variety of aryl nitriles



Entry	ArCN	X	Product	Reaction Time[a]	Yield[b]
1		TBS		16 h	84
2		TBS		5 h	92
3		TBS		2.5 h	84
4		TBS		3 h	90
5		TBS		12 h	91
6				7 h	94
7		SMe		20 min	96
8		TBS		20 min	90
9		TBS		45 min	60
10				7.5 h	98
11				45 min	93
12		Cl		7 h	69

[a] See Ref. 6 for a representative procedure; using HCl work-up, except entries 4 and 8 where AcOH was used. Alternatively, the TBS in those cases could be removed using HCl work-up.

[b] Assay yield by HPLC, as compared to chromatographed standard.

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2. For recent variations, see: (a) Lin, Y.; Seifert, C. M.; Kang, S. M.; Dusza, J. P.; Lang, S. A., Jr. *J. Heterocyclic Chem.* **1979**, *16*, 1377; (b) Knoll, A.; Liebscher, J.; Radeglia, R. *J. Prakt. Chem.* **1985**, *3*, 463; (c) Romero-Ortega, M.; Aviles, A.; Cruz, R.; Fuentes, A.; Gomez, R. M.; Plata, A. *J. Org. Chem.* **2000**, *65*, 7244; (d) Rajappa, S.; Sudarsanam, V.; Advani, B. G.; Rane, A. V. *Proc. Indian Acad. Sci.* **1982**, *91*, 445.
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4. For precedence with thiophene, see: Graham, S. L.; Scholz, T. H. *J. Org. Chem.* **1991**, *56*, 4260.
5. An excess of thiazole was used to ensure complete conversion of nitrile, though a slight excess of either substrate has been shown to effect complete reaction.
6. *Representative procedure*: 2-(*t*-Butyldimethylsilyl)thiazole (1.27 g, 9.60 mmol) was dissolved in THF (15 mL) and cooled to −60°C. *n*-BuLi (6.0 mL, 9.60 mmol, 1.6 M in hexanes) was added at such a rate as to keep the reaction temperature below −40°C, forming a deep red solution, which became a slurry. 4-Cyanopyridine (500 mg, 4.80 mmol) was dissolved in THF (3 mL) and added to the reaction, and the temperature was held between −35 and −20°C for 20 min. Aqueous AcOH (1 M, 28.8 mmol) was added, and the hydrolysis was aged overnight. The solution was diluted with EtOAc and H_2O, and the organic was washed with a 50% aq. K_2CO_3 solution (2×20 mL). After drying over Na_2SO_4, the solution was filtered and concentrated to an orange oil. The ketone was purified by column chromatography using 20% EtOAc in hexanes and isolated as a yellow oil. ^{1}H NMR (DMSO): δ 8.83 (dd, 2H, $J=4.42$, 1.61 Hz), 8.67 (s, 1H), 7.77 (dd, 2H, $J=4.42$, 1.61 Hz), 0.95 (s, 9H), 0.40 (s, 6H) ppm; ^{13}C NMR (DMSO): δ 186.4, 182.2, 152.4, 151.0, 144.4, 140.4, 122.6, 26.5, 17.0, −5.2 ppm. To remove TBS, the reaction was poured into 2N HCl and THF, aged for 1 h, and worked-up in a similar manner.
7. Analysis of reaction mixtures revealed that none of the tertiary alcohol product expected from overaddition had formed.
8. The imine stability was problematic when R = OMe, X = SMe because the HCl salt of the imine precipitated before hydrolysis was complete
9. In some cases (entries 1–3 and 9, Table 2) a slow imine hydrolysis with aq. AcOH led to some cleavage of the TBS group before imine hydrolysis was complete.