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The synthesis of 3-amino-5-arylisothiazoles from propynenitriles

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ABSTRACT

A new synthesis of 3-amino-5-arylisothiazoles is reported. The reaction is operationally simple, utilises readily synthesised propynenitriles as starting materials and is tolerant of a range of functional groups. The optimised reaction conditions can also be used with 3-chloropropenenitriles in place of propynenitriles.

Introduction

During a recent drug discovery programme a range of *N*-(5-phenyl-1,2-thiazol-3-yl)amides **3** were required (Fig. 1). These were accessed *via* acylation of the corresponding 3-amino-5-arylisothiazoles **1**. 3-Amino-isothiazoles are important heterocyclic building blocks incorporated into MCH1R antagonists and a drug used to treat schizophrenia.[1] A survey of the literature indicated that the 3-amino-5-arylisothiazole core is not well precedented. The reported syntheses require multiple steps to obtain suitable starting materials,[2] or require the use of concentrated hydrazine at elevated temperatures.[3] Hackler and co-workers reported the synthesis of 3-amino-5-*t*-butylisothiazole **6** from *Z*-3-chloro-4,4-dimethyl-2-pentenenitrile **4** albeit in low yield (Scheme 1, *i*).[4] We presumed this route would also be applicable to 3-chloro-3-phenylprop-2-enenitrile **7** and were pleased to isolate the desired product using the same conditions (Scheme 1, *ii*). As we continued to synthesise a range of analogues we found that the synthesis of a range of substituted 3-chloro-3-phenylprop-2-enenitriles were low yielding and somewhat capricious and therefore sought a more reliable route.

We envisaged the addition of sodium sulfide to 3-phenylpropiolonitrile **9** would generate a thioketoenolate similar to **5**. Propynenitriles are readily synthesised *via* a variety of methods, including cyanation of alkynes,[5] reaction of aldehydes with trichloroacetonitrile and base,[6] and dehydration of benzoylacetonitriles with Mukaiyama's reagent.[7] Gratifyingly, the initial reaction using Hackler's conditions yielded aminoisothiazole **8** in comparable yield (Scheme 2).

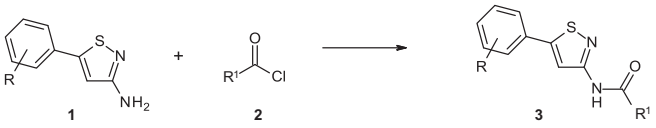
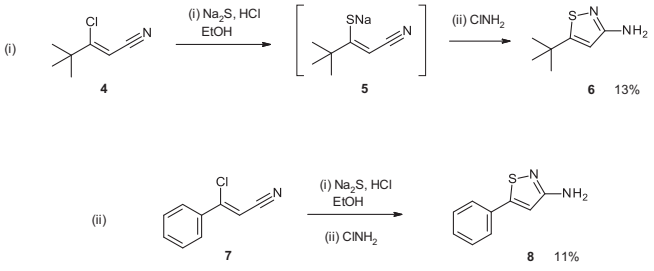
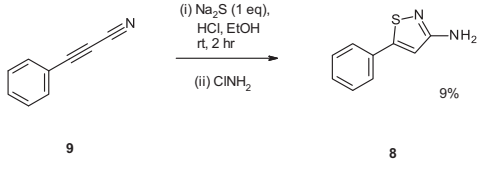


Figure 1. Synthesis of *N*-(5-phenyl-1,2-thiazol-3-yl)amides.



Scheme 1. Initial synthesis of 3-amino-isothiazoles.



Scheme 2. Reaction of 3-phenylpropiolonitrile.

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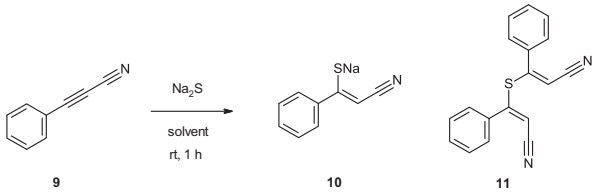
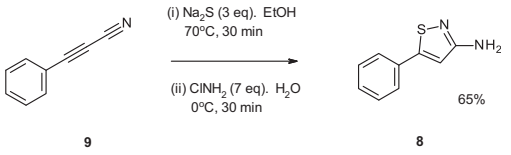
Table 1
Optimization of sulfide addition.[a]



Entry	Na_2S (eq.)	Solvent	**9** (%)	**10** (%)	**11** (%)
1	1	EtOH	34	16	50[b]
2	1	EtOH	11	40	49
3	2	EtOH	8	62	30
4	3	EtOH	7	70	23
5	4	EtOH	7	74	19
6	5	EtOH	7	76	17
7	3	MeOH	12	61	27
8	3	MeOH/Water (1:1)	12	58	30
9	3	Water	100	0	0
10	3	DMF	37	5	3
11	3	NMP	32	26	13
12	3	EtOH	11	89	0[c]

[a] Reaction conditions: A solution of 3-phenylpropiolonitrile was added to a stirred suspension of sodium sulfide. Reaction stirred at rt for 1 h then analysed by LCMS.
[b] Sodium sulfide added to a stirred solution of 3-phenylpropiolonitrile.
[c] Reaction stirred at 70 °C.



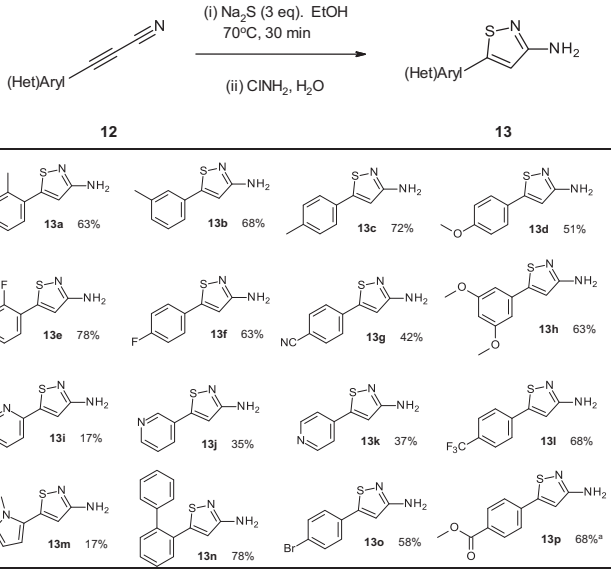
Scheme 3. Optimised reaction conditions.[9]

With this result in hand, optimisation of the reaction conditions using readily available 3-phenylpropiolonitrile **9** was investigated (Table 1). Initially this optimisation focused on the addition of sodium sulfide to generate thioketoenolate **10**. Intermediate **10** is unstable to isolation but could be detected by LCMS in the crude reaction mixture.[8] Analysis of the reaction mixture after the addition of sodium sulfide showed two new products were formed; one was the desired thioketoenolate (**10**) and the other was a dimeric species (**11**).

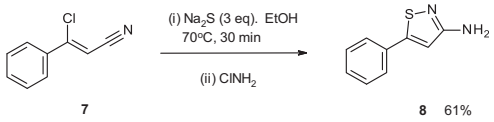
Varying the order of addition (Table 1, Entries 1 and 2) and increasing the number of equivalents of sodium sulfide (Entries 3 to 6) resulted in a higher yield of **10**, however significant amounts of **11** remained. Changing the solvent to MeOH and MeOH/water gave comparable yields to EtOH (Entries 7 and 8), while other solvents resulted in lower yields and multiple by-product formation (Entries 9 to 11). A significant discovery was that heating the reaction to 70 °C for 30 min improved the ratio of **10**:**11**, presumably the elevated temperature allowed the excess sodium sulfide to react with **11** to generate **10** in good yield (Entry 12). Optimisation of the second step revealed that 7 equivalents of chloramine were necessary to convert the intermediate to the desired product in reasonable yield (Scheme 3).

The optimised conditions were used to explore the substrate scope of the reaction (Table 2). The reaction is tolerant of electron withdrawing and donating groups, halogens, esters and nitriles. Heterocycles were also tolerated albeit with a reduced yield.

Table 2
Substrate scope.



[a]MeOH at reflux used in place of EtOH to prevent transesterification.



Scheme 4. Optimised reaction conditions using 3-chloro-3-phenylprop-2-enenitrile.

Finally, 3-chloro-3-phenylprop-2-enenitrile **7** was re-examined as a starting material under the optimised reaction conditions. Pleasingly, the desired product **8** was isolated in an improved 61% yield (Scheme 4), demonstrating that 3-amino-5-arylisothiazoles can be accessed from either starting material depending on availability.

In summary, we have developed reaction conditions which enable the synthesis of 3-amino-5-arylisothiazoles from either propynenitriles or 3-chloro-3-phenylprop-2-enenitriles. The reaction is fast, operationally simple and compatible with a broad range of substrates.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2018.01.042

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9. Typical experimental procedure: *5-phenylisothiazol-3-amine* (***8***). A solution of 3-phenylpropiolonitrile (100 mg, 0.79 mmol) in EtOH (4 mL) was added to a stirred suspension of sodium sulfide (184 mg, 2.36 mmol) in EtOH (4 mL). The resulting reaction was stirred at 70 °C for 30 min then cooled to 0 °C. In a separate flask sodium hypochlorite (4–6% in water) (7.57 mL, 5.51 mmol) was added to ice cooled ammonia (28–30% in water, 7.1 mL, 110 mmol). The reaction was stirred at 0 °C for 15 min then added to the contents of the first reaction. The reaction was stirred at 0 °C for 30 min. The reaction mixture was diluted with DCM (50 mL), and washed sequentially with water (25 mL) and saturated brine (25 mL). The organic layer was dried with $MgSO_4$, filtered and evaporated to afford the crude product. The crude product was purified by flash silica chromatography, elution gradient 20–80% EtOAc in heptane to afford 5-phenylisothiazol-3-amine (90 mg, 65%) as a yellow solid. ^{1}H NMR (500 MHz, DMSO) 6.14 (s, 2H), 6.81 (s, 1H), 7.39–7.48 (m, 3H), 7.55–7.6 (m, 2H). HRMS $(M + H)^+$: Found: 177.0491 Calc: 177.0486.