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# Malononitrile as a carbonyl synthon: a one-pot preparation of heteroaryl amide via a $S_NAr$-oxidation–displacement strategy ☆

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**Abstract**—Malononitrile could be utilized as a synthon for the carbonyl moiety via a one-pot process that was initiated via base-mediated $S_NAr$ substitution of a heteroaryl halide. Subsequent peracetic acid oxidation of the resultant anion delivered an electrophilic acyl nitrile in situ that readily reacted with added nucleophiles to afford heteroaryl carboxylic acid derivatives. The reaction of the sodium salt of malononitrile with a series of heteroaryl chlorides followed by the subsequent addition of an amine and peracetic acid provided the corresponding heteroaryl amides.


Heteroaryl amides are useful synthetic intermediates[1] and are also prominent structural elements of several drugs,[2] including the antiarthritic leflunomide and the antiemetic agent geranisetron (Fig. 1). We have previously demonstrated that heterocyclic *N*-acetonitrile derivatives **1** could be utilized as ambient synthons for the carbonyl moiety **2** (Fig. 2).[3] As shown in Scheme 1, the anion of an azole-*N*-acetoacetonitrile **1** was generated using a strong base such as NaHMDS and then reacted with a heteroaryl halide **3** to form the substituted aminoacetonitrile derivative **4**. After oxidation of **4**, the intermediate acylated azole **5** reacted readily with

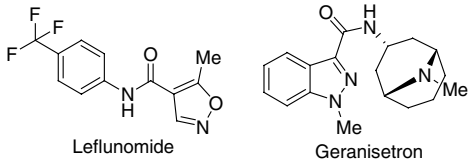


**Figure 1.**

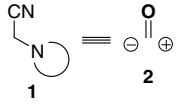


**Figure 2.**

an amine or alcohol in situ to afford the heteroaryl amide or ester **6**, respectively.

In an effort to further define the scope of this process, we identified several shortcomings that provided some limitations on the application of this procedure as a synthetic methodology. Of particular concern was the necessity for the use of strong bases to remove the α-protons, which limits compatibility with a wider range of functionality.[3,4] In addition, those heterocyclic *N*-acetonitrile derivatives **1** available from commercial sources are generally expensive while the synthesis of individual reagents is inconvenient.

With these concerns in mind, we examined the potential of malononitrile (**7**) to replace the azole-*N*-acetonitrile as the linchpin in this synthetic protocol, a process summarized in Scheme 2. Thus, it was anticipated that heteroarylation of the anion of malononitrile (**7**) would provide the anion of **8**, which would lead to the acyl nitrile **9** after oxidation in situ.[5] Acyl nitriles are electrophilic,[6] with cyanide functioning as an excellent leaving

*Keywords*: Carboxamide synthon; Heteroaryl amide; Condensation–oxidation; Malononitrile.
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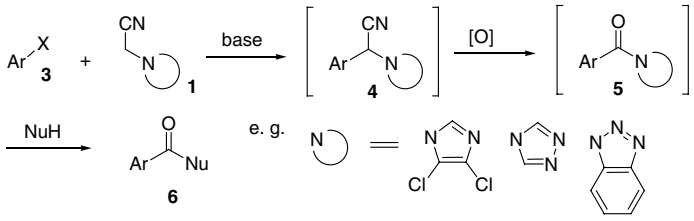
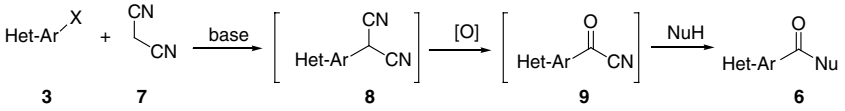



**Scheme 1.**



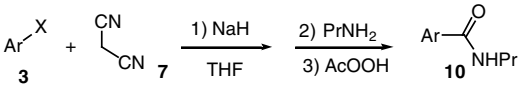

**Scheme 2.**

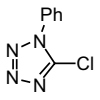
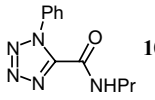
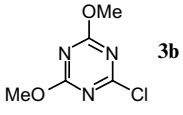
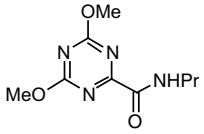
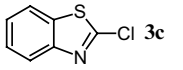
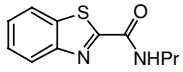
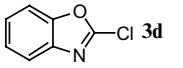
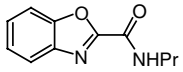
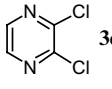
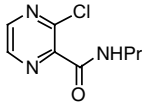
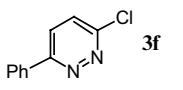
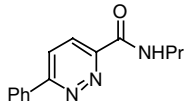
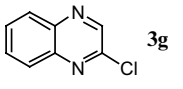
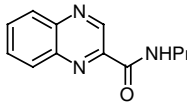
group that is readily displaced by a range of nucleophiles to afford a carboxyl derivative **6**. Malononitrile (**7**) offers several advantages when compared to azole-*N*-acetonitrile derivatives: the methylene protons are much more acidic, p$K_a$∼11 in $H_2O$ or DMSO,[7] which would allow the use of much weaker bases to effect deprotonation; malononitrile (**7**) is commercially available and inexpensive; conditions for reacting malononitrile with a broad range of electrophiles, including hydrocarbon aromatics, are well-established.[8]

Using **3c** and **3g** as the heteroaryl chlorides, a survey of bases and oxidants quickly established that NaH and peracetic acid were effective reagents for the respective reactions, providing an overall process of sequential $S_NAr$ substitution, oxidation and acylation similar to the previously demonstrated protocol that relied upon an azole-*N*-acetonitrile **1**.[3] The scope of this protocol was examined by reacting malononitrile (**7**), taken in three or more fold excess, with a series of heteroaryl chlorides **3** in the presence of 2 equiv of NaH followed sequentially by *n*-propyl amine and then AcOOH, which afforded the corresponding heteroaryl *n*-propylamide derivatives **10** in yields ranging from 29% to 67%. The specific examples compiled in Table 1 demonstrate the range of heteroaryl chlorides that readily participate in this process.[9,10] An excess of malononitrile was found to be essential in order to ensure complete consumption of the heteroaryl chloride in a process that required extended reaction time when compared to the more reactive azole-*N*-acetonitrile where the $S_NAr$ step was typically completed in as little as 2 h.

In summary, malononitrile (**7**) has been established as an effective carbonyl synthon in a process that takes advantage of inherent ambient reactivity that can be revealed in a controlled fashion. The concept of exploiting malononitrile (**7**) as a synthetic linchpin allows the construction of heteroaryl amides using a convenient reaction protocol that is simple to execute and does not require the preparation of unique or custom reagents. While some of the yields are modest, the convenience of conducting three discrete steps comprising of the straightforward addition of reagents to a single reaction vessel provides significant compensation. The extension of this methodology to the synthesis of hydrocarbon-based aromatic amides from aryl halides using transition metal-mediated cross coupling to effect the $S_NAr$ step of the process is under active investigation.

**Table 1.** Preparation of *n*-propyl *N*-heteroaryl amides from heteroaryl chlorides and malononitrile




| Entry | Ar–X **3** | Product **10** with isolated yield |
|---|---|---|
| 1 |  **3a** |  **10a**, 47% |
| 2 |  **3b** |  **10b**, 65% |
| 3 |  **3c** |  **10c**, 53% |
| 4 |  **3d** |  **10d**, 67% |
| 5 |  **3e** |  **10e**, 30% |
| 6 |  **3f** |  **10f**, 29% |
| 7 |  **3g** |  **10g**, 48% |

## Supplementary material

The supplementary data is available online in ScienceDirect, including $^{1}H$ and $^{13}C$ spectra and HRMS data of compounds **10a**–**g**.

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9. *A general procedure: Preparation of compound **10b***. A mixture of malononitrile (**7**) (339 mg, 5.13 mmol) and NaH (60% in oil, 412 mg, 10.3 mmol) in dry THF (15 mL) was stirred at room temperature under $N_2$ for 10 min before adding 2-chloro-4,6-dimethoxy-1,3,5-triazine **3b** (300 mg, 1.71 mmol). The reaction mixture was stirred at room temperature for 12 h before adding propyl amine (0.28 mL, 3.42 mmol). After 5 min, peracetic acid (32% wt in acetic acid, 812 mg, 3.42 mmol) was added and the mixture stirred for 15 min before being quenched with $NaHSO_3$ (1 g), The reaction mixture was partitioned between $NaHCO_3$ and EtOAc, the layers separated and the aqueous phase extracted with EtOAc. The combined organic layer was dried over $MgSO_4$, concentrated and the residue purified by silica gel chromatography to afford **10b** (250 mg, 65%) as a yellowish oil.
10. The reaction and the subsequent work-up should be undertaken with care in a well ventilated hood due to the potential for HCN to be liberated.