Azole-*N*-Acetonitriles as Carbonyl Synthons: A One-Pot Preparation of Heteroaryl Amides from Halides

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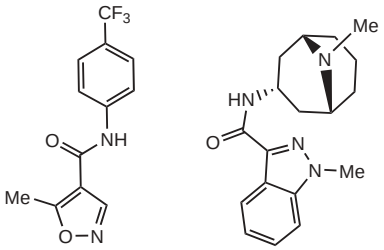
Received 17 June 2004

Abstract: Azole-*N*-acetonitrile derivatives were utilized as synthons for an ambident carbonyl moiety via a strategy relying upon sequential base-mediated S_NAr substitution of a 2-halo heterocycle, in situ oxidation, and amine displacement. This strategy allows prompt and efficient synthesis of N-containing heteroaryl amides directly from the corresponding halides via a one-pot process.

Key words: azole-*N*-acetonitrile, carbonyl synthon, heteroaryl amide, acyl anion equivalent

Heteroaryl amides are commonly encountered as structural elements in many investigational and marketed drugs. Two prominent examples of the latter are the antiarthritic agent Leflunomide and the antiemetic agent Granisetron (Figure 1).[1,2] We have previously demonstrated that N,N-disubstituted aminoacetonitrile derivatives **1** are effective and versatile synthons for amides of general composition **2**[3] and that an aryl acetonitrile, represented by **3**, can be viewed as the synthetic equivalent of an aryl carbonyl moiety **4** (Figure 2).[4] For both, a two-step process consisting of base-mediated alkylation of the methylene moiety and subsequent oxidation results in the generation of the final carbonyl moiety **10** or **11** after elimination of HCN from an intermediate cyanohydrin **8** or **9**. This process is summarized in Scheme 1.[3,4]



Leflunomide Granisetron

Figure 1 Marketed drugs with amide subunits

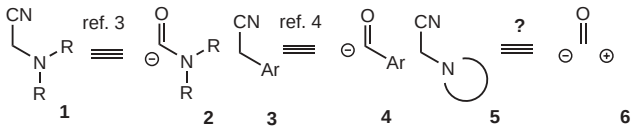
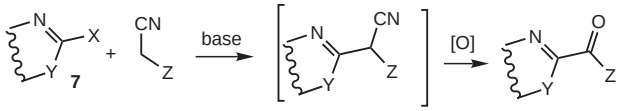


Figure 2 Carbonyl synthons



Scheme 1 Preparation of heteroaryl amides or heteroaryl ketones via a condensation–oxidation-displacement protocol

However, two issues remain to be addressed. First, it is readily apparent that in both of these protocols, the substituent bound to the acetonitrile moiety is retained in the final product, providing some limitation to the versatility of the reaction, which only allows constructing amides or ketones along one dimension. Second, the claim 'aminoacetonitrile derivatives as amide synthons' is restricted to N,N-disubstituted aminoacetonitrile derivatives **1**. When N-monosubstituted aminoacetonitriles were applied, cyano-imine derivatives, rather than primary amides, were generated.[3b] Such results showed that the procedure described in Scheme 1 is only capable of producing secondary amides.

As part of an effort to further broaden the utility of this synthetic protocol it was envisioned that if the amine element of structure **1** could be configured to act as a leaving group, substituted acetonitriles represented by **5** would function in an ambident fashion, acting sequentially in a nucleophilic and an electrophilic capacity, thereby delivering a synthetic equivalent to **6** (Figure 2). This approach would permit building amides two-directionally, offering a very efficient method for the preparation of N-containing heteroaryl amides, including both primary and secondary amides, directly from the corresponding halides, respectively. The documented one-pot process, possessing similar capability, has been limited to transition-metal-mediated amidation of aryl halide with carbon monooxide and amine, which generally requires escalated temperature and/or high pressure.[5]

The realization of this protocol relies upon the fact that acyl derivatives of sp^2-hybridized azole nitrogen atoms (**12**) are, in contrast to simple amides derived from sp^3-configured nitrogen atoms, chemically labile and well established as acylating agents (Figure 3).[6] In previous studies, we have established synthetic access to stable substituted acetonitriles **8** derived from simple amine derivatives and demonstrated that they could readily be oxidized to amides **10**.[3,4] Consequently, the extension of this

SYNLETT 2004, No. 13, pp 2323–2326
Advanced online publication: 28.09.2004
DOI: 10.1055/s-2004-832849; Art ID: S05604ST

chemistry to aminoacetonitriles **13** derived from an azole of the type depicted in Figure 3 became the objective, with the concept summarized in Scheme 2.

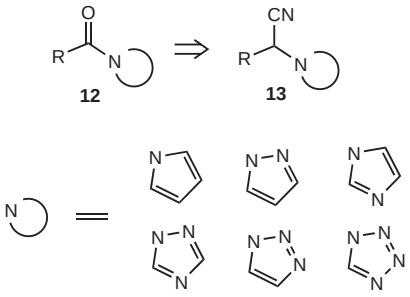
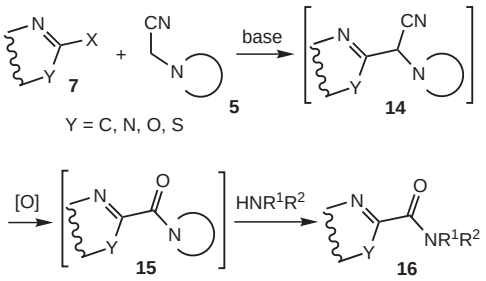


Figure 3 Amide derived from aminoacetonitrile

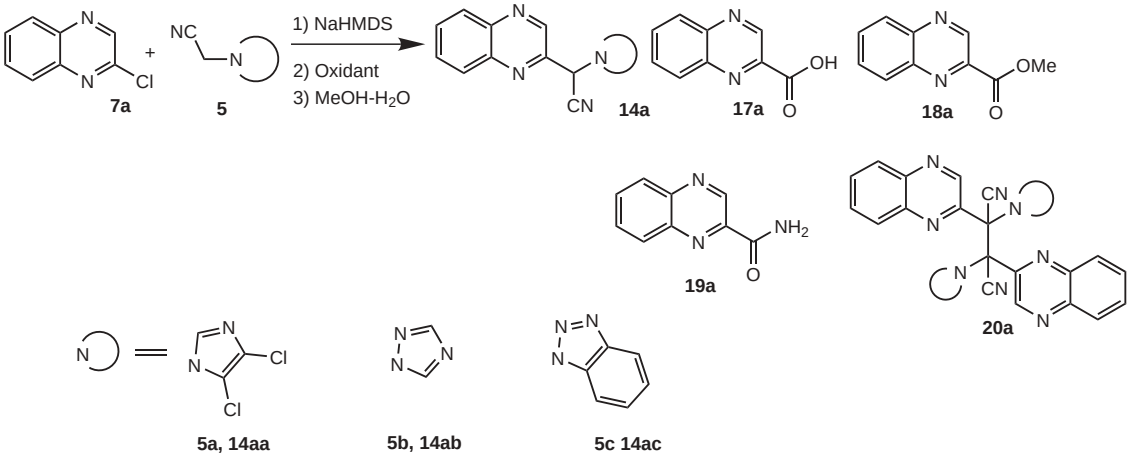
It was anticipated that an anion generated from an azole-*N*-acetonitrile **5** using a strong base, such as NaHMDS, would react with a heteroaryl halide **7** via an *ipso*-displacement process to form the substituted aminoacetonitrile derivative **14**. The subsequent oxidation of **14** to the corresponding cyanohydrin would set the stage for elimination of HCN to afford an acylated azole derivative **15** that as an activated carbonyl derivative would react with an exogenous amine to provide the heteroaryl amide **16**.



Scheme 2 Preparation of heteroaryl amides via a condensation–oxidation–displacement protocol

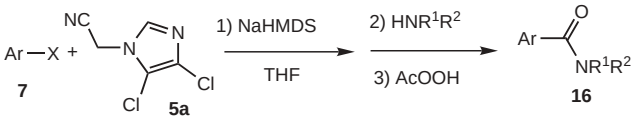
In order to explore the viability of the proposed *ipso*-displacement–oxidation sequence, a series of three commercially available azole-*N*-acetonitrile derivatives **5** were examined using the quinoxaline chloride **7a** as the other reaction partner in conjunction with a concomitant survey of potential oxidants. A mixture of **5a**, **5b**, or **5c** and **7a** in THF at room temperature was treated with 2.5 equivalents

Table 1 Investigation of Possible Leaving Groups and Oxidants

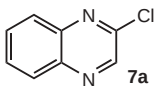
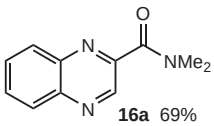
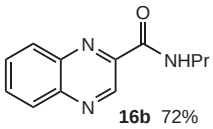
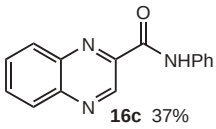
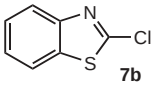
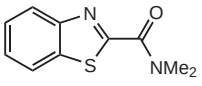
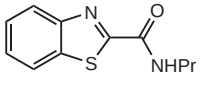
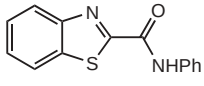
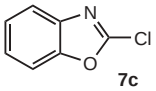
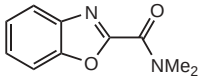
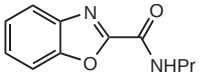
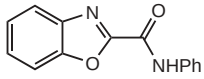
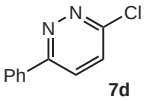
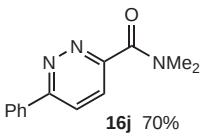
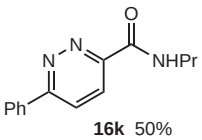
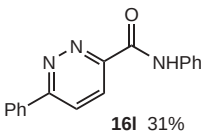


Entry	Oxidant	Product (LC-MS yield, %) from **5a**	Product (LC-MS yield, %) from **5b**	Product (LC-MS yield, %) from **5c**
1	AcOOH	**19a** (80)	**19a** (85)	**19a** (61)
2	*t*-BuOOH	**14aa** (87)	**14ab** (89) **19a** (4)	**14ac** (89)
3	TMSO-OTMS	**14aa** (46) **19a** (46)	**18a** (31) **19a** (47)	**14ac** (18) **19a** (32)
4	Bleach	**19a** (15) **20a** (21)	**20a** (36)	Complicated mixture
5	*m*CPBA	**19a** (80)	**19a** (70)	**19a** (66)
6	NiO_2–H_2O	**14aa** (53) **18a** (2) **19a** (10) **20a** (10)	**14ab** (45) **20a** (19)	NA
7	Na_2O_2	**14aa** (82)	**14ab** (91)	NA

Table 2 One-Pot Synthesis of N-Containing Heteroaryl Amides



7 **5a** **16**

	Me_2NH	Yield (%)	*n*-$PrNH_2$	Yield (%)	$PhNH_2$	Yield (%)
 **7a**	 **16a** 69%	69	 **16b** 72%	72	 **16c** 37%	37
 **7b**	 **16d** 78%	78	 **16e** 74%	74	 **16f** 32%	32
 **7c**	 **16g** 87%	87	 **16h** 63%	63	 **16i** 41%	41
 **7d**	 **16j** 70%	70	 **16k** 50%	50	 **16l** 31%	31

of NaHMDS followed 30 minutes later by the addition of an excess of oxidant. The reaction mixture was quenched by the addition of MeOH and H_2O and the product mixtures identified by LC-MS. The results are compiled in Table 1. Somewhat surprisingly, the amide **19a** emerged as the preferred product in most of cases instead of the expected acid **17a** or ester **18a**. This result substantiated the feasibility of the proposed protocol but suggested that either HMDS or derived ammonia had successfully and effectively competed with MeOH and H_2O as the nucleophile towards the acylated azole intermediate.[7] With respect to potential oxidants, AcOOH (entry 1, Table 1) and *m*CPBA (entry 5, Table 1) provided the cleanest results with the other agents examined performing significantly less effectively. Competitive dimerization occurred during oxidation with either NiO_2 or bleach, producing compound **20a** and implicated the involvement of radical-based mechanisms in these specific examples (entries 4 and 6, Table 1).

Based on the observed yield, ease of handling and commercial availability, peracetic acid was selected as the preferred oxidant for subsequent studies of the scope of the process. 2,3-Dichloroimidazole was selected as the reaction partner in further studies although all of the heterocycles probed, 2,3-dichloro imidazole, 1,2,4-triazole and benzotriazole, behaved similarly and were suitable substrates for the process.

In order to avoid the competition for the acylated azole by HMDS, a revised protocol in which an amine was added prior to the oxidant was developed. The results of a survey of this process, conducted using four heteroaryl chlorides and three amine derivatives that provided a series of heteroaryl amides **16**, are summarized in Table 2.[8,9] Primary (products **16b**, **16e**, **16h**, **16k**, Table 2) and secondary (products **16a**, **16d**, **16g**, **16j**, Table 2) aliphatic amines participated effectively, generally providing the products in greater than 50% yield. The poorly nucleophilic amine aniline produced anilides in only moderate yields, 30–40% (products **16c**, **16f**, **16i**, **16l**, Table 2).

In summary, we have demonstrated the feasibility of azole-*N*-acetonitriles derivatives as carbonyl synthons[10] based on a protocol that takes advantage of sequential ambident chemical reactivity. The synthetic sequence allows for versatility in the selection of both the heteroaryl halide that participates in the initial displacement reaction and the amine moiety that intercepts the acylated azole intermediate. 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.

Acknowledgment

The authors would like to thank Mr. Alan Xiang-dong Wang for valuable discussion, and Dr. Li Pan and Dr. Xiaohua Stella Huang for assistance in obtaining exact mass and NMR spectral data.

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(7) This assumption was further confirmed with an addition of excess of EtOH prior to oxidation under the same condition. The formation of **19a** (51%) and the ethyl ester (31%) was detected by LC-MS.

(8) **General Procedure for the Preparation of Heteroaryl Amides:** NaHMDS (2.5 mL, 1.0 M in THF, 2.5 mmol) was added into a solution of 2-chloro-benzooxazole (153 mg, 1.0 mmol), and (4,5-dichloro-imidazol-1-yl)-acetonitrile (264 mg, 1.5 mmol) in dry THF (15 mL). After stirring for 10 h at r.t. dimethylamine (1.5 mL, 2 M in THF, 3.0 mmol) and HOOAc (0.84 mL, 32 wt.% in HOAc, 4.0 mmol) were subsequently added and the mixture stirred a further 10 h at r.t. The reaction mixture was quenched with sat. Na_2SO_3 solution and neutralized by sat. $NaHCO_3$ solution, the aqueous layer extracted with EtOAc (3×20 mL) and the combined organic layer dried over $MgSO_4$. Concentration in vacuo afforded a residue which was purified by silica gel chromatography to provide benzoxazole-2-carboxylic acid dimethylamide (**16g**, 165 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.71 (d, 1 H, J = 8.0 Hz), 7.52 (d, 1 H, J = 8.0 Hz), 7.33 (m, 2 H), 3.39 (s, 3 H), 3.10 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.6, 155.2, 149.9, 140.3, 127.0, 125.2, 121.2, 111.4, 38.8, 36.4. HRMS: *m/z* $[M + H]^+$ calcd for $C_{10}H_{11}N_2O_2$: 191.0821; found: 191.0824.

(9) The reaction and the subsequent work-up should be undertaken with care in a well-ventilated hood due to the possibility of HCN liberation.

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