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A one-pot synthesis of nitrogen-containing heteroaryl α-keto amides from heteroaryl halides

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Abstract—The S_NAr-type reaction of the piperidine amide of cyanoacetic acid with a series of heteroaryl halides followed by in situ oxidation of the resultant anion with peracetic acid provided a convenient, one-pot protocol for preparative access to heteroaryl α-keto amides. In this procedure, the amide of cyanoacetic acid functions as an Umpolung-type synthon of the α-keto amide moiety.

Heteroaryl α-keto amides are of interest to both the synthetic organic and medicinal chemistry communities with representatives displaying a range of biological properties.[1] A common approach toward the synthesis of α-keto amides **1** depends upon the coupling reaction of a glyoxylic acid derivative **2** with an amine **3**, as depicted in Route A, Scheme 1. However, while straightforward in concept, this route is limited by the commercial availability of the glyoxylic acid derivative **2**, thereby restricting the structural diversity of the α-keto amides available by this strategy. An alternative protocol, summarized in Route B, Scheme 1, relies upon the reaction of more readily available esters **5** with the anion of an α-aminoacetonitrile **6** followed by oxidation of the intermediate **4**.[2] In this process, α-aminoacetonitrile **6** functions as an Umpolung-type synthon of the amide anion **7**.[2] As an extension of our interest in developing synthetic access to α-keto amide derivatives,[2] we now describe the results of our efforts to develop a practical preparative procedure that relies upon a third topological retrosynthetic disconnection, summarized in Route C, Scheme 1. This strategy complements that of Route B in Scheme 1 by its dependence on a sequence of S_NAr-type condensation of an aminocarbonylacetonitrile **10** with an aryl or heteroaryl halide **9**[3,4] to afford the anion of **8** that is oxidized[5] to afford a cyanohydrin that would be expected to collapse to the corresponding α-keto amides **1**. In this process, amide **10** effectively functions as an Umpolung-type equivalent of anion **11**. Precedent for the S_NAr step, both as a simple displacement by the anion of **10**[3] or under transition metal-catalyzed conditions,[4] suggested the practical feasibility of this reaction. However, the oxidation of cyanoalkane derivatives to cyanohydrins, as well their collapse to carbonyl derivatives, has often proven to be somewhat unpredictable and challenging.[5,6] In the process envisaged, the anion of **8** is stabilized by three distinct electron deficient substituents and as such may be anticipated to react somewhat sluggishly toward an oxidant. Consequently, a reliable procedure for the in situ oxidation of the anion of the primary product **8** to a cyanohydrin and collapse to liberate HCN[7] and target α-keto amide **1** was essential.

In order to establish the viability of the proposed protocol, the concept was investigated by reacting heteroaryl chlorides **9a**, **b**, or **c** with 1-cyanoacetylpiperidine **10a** under S_NAr reaction conditions. NaH, NaHMDS, K_2CO_3, and K-*O*^{t}Bu were evaluated as potential bases in the initial survey with the result that at room temperature both NaH and NaHMDS provided for a clean S_NAr displacement. In contrast, K_2CO_3 failed to promote the desired reaction and K-*O*^{t}Bu competed with the anion of **10a** as a nucleophile and was thus deemed unsuitable. A variety of reagents were examined in order to establish the optimum conditions for the oxidative

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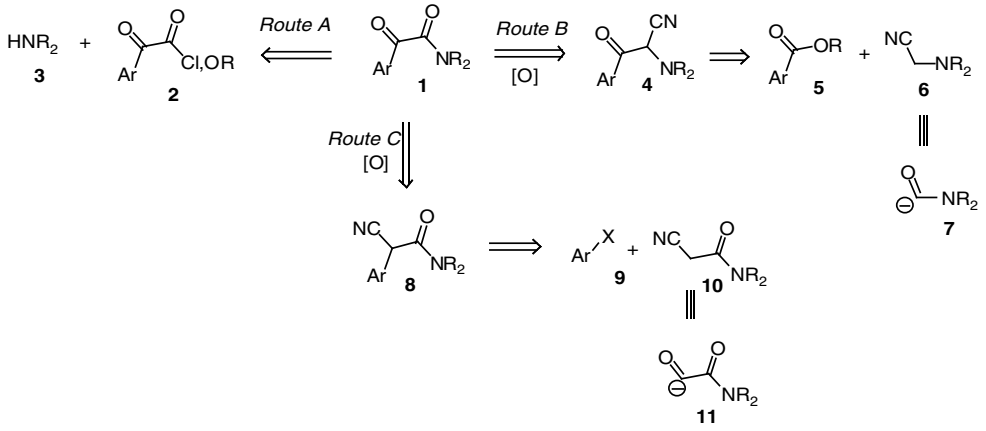


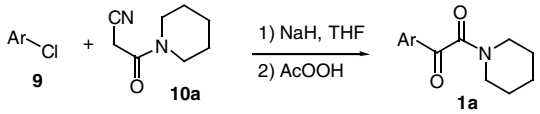
Scheme 1. Approaches to the synthesis of α-keto amides.

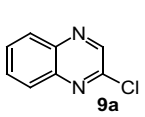
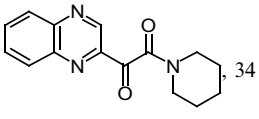
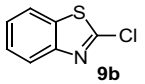
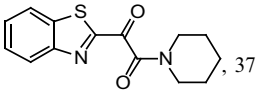
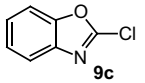
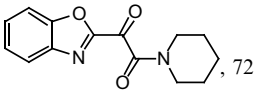
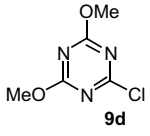
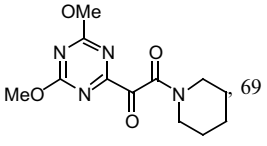
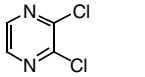
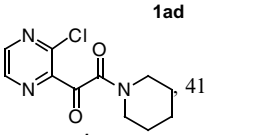
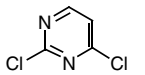
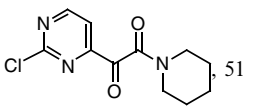
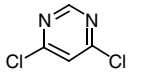
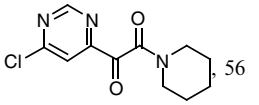
removal of cyanide, including peracetic acid, *m*-CPBA, Clorox™, oxone, NiO_2–H_2O, Na_2O_2, TMSO–OTMS, BaO_2, MgO_2, CaO_2, SrO_2, ZnO_2, Li_2O_2, MnO_2, *t*-BuOOH, $NaBO_3{\cdot}4H_2O$, and sodium carbonate peroxide. However, of these, only *m*-CPBA and peracetic acid proved to be effective, with intermediate **8** typically resistant to oxidation by all of the other agents. This result presumably reflects the stabilization afforded anion **8** by the three electron withdrawing substituents. Based on ease of handling, NaH was selected as the preferred base along with peracetic acid as the oxidant for subsequent studies designed to explore the scope of the process. As can be seen from the survey summarized in Table 1, several additional heteroaryl halides readily participate as reaction partners providing α-keto amide derivatives in modest to good yield in a convenient, one-pot procedure. Of particular note, the heterocycles **9e**–**g**, which incorporate two leaving groups, provide products of mono-substitution in yields quite acceptable for a 2-step process. The displacement of the second of the chlorine atoms in **9e**–**g** is presumably impeded by the anionic nature of the product **8** and the attendant partial delocalization of charge into the heterocycle ring.

A general procedure is exemplified with the preparation of compound **1ad**. A mixture of 1-cyanoacetylpiperidine **10a** (2.5 equiv) and NaH (3.5 equiv) in dry THF was stirred at room temperature for 10 min under an atmosphere of N_2. 2-Chloro-4,6-dimethoxy-1,3,5-triazine **9d** (1.0 equiv) was added and the reaction mixture stirred for 16 h at room temperature. Peracetic acid (32% wt in acetic acid, 2 equiv) was injected cautiously into the solution at such a rate that the internal temperature was maintained below 25 °C. The resultant mixture was stirred for an additional 2 h, quenched with $NaHSO_3$ (10 equiv), and partitioned between saturated aqueous $NaHCO_3$ and EtOAc. The aqueous phase was extracted with EtOAc and the combined organic layer dried over $MgSO_4$. Concentration and purification of the residue by silica gel chromatography afforded piperidinyl (4,6-dimethoxy-1,3,5-triazin-2-yl)glyoxylylamide **1ad**[8] as a white solid in a yield of 69%.

In summary, the secondary amide of cyanoacetic acid **10** can be considered as an effective Umploung-type

Table 1. The preparation of α-keto amides from nitrogen-containing heteroaryl chlorides



Entry	Ar–Cl **9**	Product, %
1	 **9a**	 , 34 **1aa**
2	 **9b**	 , 37 **1ab**
3	 **9c**	 , 72 **1ac**
4	 **9d**	 , 69 **1ad**
5	 **9e**	 , 41 **1ae**
6	 **9f**	 , 51 **1af**
7	 **9g**	 , 56 **1ag**

synthon for the carbanion **11** (Scheme 1). The anion of **10** participates readily in a S_NAr-type reaction with heteroaryl halides to afford a stabilized anion that is susceptible to oxidation by peracetic acid with the resultant cyanohydrin collapsing to the corresponding *N*,*N*-disubstituted heteroaryl glyoxamide derivative. The overall process allows for the construction of nitrogen-containing heteroaryl α-keto amides from the corresponding heteroaryl halides in a convenient, one-pot preparative protocol. The extension of this methodology to the synthesis of hydrocarbon-based aromatic amides from aryl halides is under active investigation and will be described in due course.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.100.

References and notes

1. (a) Wang, T.; Zhang, Z.; Wallace, O. B.; Deshpande, M.; Fang, H.; Yang, Z.; Zadjura, L. M.; Tweedie, D. L.; Huang, S.; Zhao, F.; Ranadive, S.; Robinson, B. S.; Gong, Y.-F.; Ricarrdi, K.; Spicer, T. P.; Deminie, C.; Rose, R.; Blair, W. S.; Lin, P.-F.; Colonno, R. J.; Meanwell, N. A. *J. Med. Chem.* **2003**, *46*, 4236; (b) Armistead, D. M.; Boger, J. S.; Meyers, H. V.; Saunders, J. O.; Tung, R. D. WO-199200278, 1992; (c) Steiner, J. P.; Snyder, S.; Burnett, A. L. WO-2002096420, 2002; (d) Magal, E. WO-199914998, 1999; (e) Fuji, M. WO-2002070491, 2002; (f) Failli, A. A.; Dusza, J. P.; Trybulski, E. J.; Memoli, K. A.; Shumsky, J. S. WO-2002085907, 2002; (g) Slassi, A.; Edwards, L.; O'Brien, A.; Meng, C. Q.; Xin, T.; Seto, C.; Lee, D. K. H.; MacLean, N.; Hynd, D.; Chen, C.; Wang, H.; Kamboj, R.; Rakhit, S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1707; (h) Black, D. StC.; Kumar, N.; McConnell, D. B. *Tetrahedron* **2000**, *56*, 8513; (i) Couve-Bonnaire, S.; Carpentier, J.-F.; Castanet, Y.; Mortreux, A. *Tetrahedron Lett.* **1999**, *40*, 3717.
2. Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2002**, *4*, 1103.
3. (a) Forbes, I. T.; Morgan, H. K. A.; Thompson, M. *Synth. Commun.* **1996**, *26*, 745; (b) El-Kousy, S. *Pharmazie* **1994**, *49*, 480; (c) L'abbe, G.; Bastin, L.; Dehaen, W.; Toppet, S.; Delbeke, P.; Vlieghe, D.; Van Meervelt, L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2545; (d) Klemm, L. H.; Muchiri, D. R.; Anderson, M.; Salbador, W.; Ford, J. *J. Heterocycl. Chem.* **1994**, *31*, 261; (e) El-Gendy, Z. *Indian J. Chem., Sect. B* **1994**, *33*, 326; (f) Hamamichi, N. *Tetrahedron Lett.* **1991**, *32*, 7415; (g) Ohba, S.; Konno, S.; Yamanaka, H. *Chem. Pharm. Bull.* **1991**, *39*, 486; (h) Borror, A. L.; Haeberer, A. F. *J. Org. Chem.* **1965**, *30*, 243.
4. (a) You, J.; Verkade, J. G. *J. Org. Chem.* **2003**, *68*, 8003; (b) Gao, C.; Tao, X.; Qian, Y.; Huang, J. *Synlett.* **2003**, 1716; (c) Suzuki, H.; Abe, H.; Thiruvikraman, S. V. *J. Org. Chem.* **1994**, *59*, 6116; (d) Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 7606; (e) Sakamoto, T.; Katoh, E.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 1664; (f) Uno, M.; Seto, K.; Ueda, W.; Masuda, M.; Takahashi, S. *Synthesis* **1985**, 506; (g) Osuka, A.; Kobayashi, T.; Suzuki, H. *Synthesis* **1983**, 67.
5. (a) Yin, Z.; Zhang, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *J. Org. Chem.* **2004**, *69*, 1364; (b) Zhang, Z.; Yin, Z.; Kadow, J. F.; Meanwell, N. A.; Wang, T. *J. Org. Chem.* **2004**, *69*, 1360; (c) Hamada, H.; Tanaka, T.; Furuya, T.; Takahata, H.; Nemoto, H. *Tetrahedron Lett.* **2001**, *42*, 909; (d) Parker, K. A.; Kallmerten, J. *J. Org. Chem.* **1980**, *45*, 2614; (e) Masuyama, Y.; Ueno, Y.; Okawara, M. *Chem. Lett.* **1977**, 1439; (f) Selikson, S. J.; Watt, D. S. *Tetrahedron Lett.* **1974**, *15*, 3029; (g) Selikson, S. J.; Watt, D. S. *J. Org. Chem.* **1975**, *40*, 267; (h) Wroble, R. R.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 2939; (i) Kuchar, M.; Brunova, B.; Rejholec, V.; Jelinkova, M.; Holubek, J.; Nemecek, O. *Collect. Czech. Chem. Commun.* **1984**, *49*, 122; (j) Grossman, R. B.; Ley, S. V. *Tetrahedron* **1994**, *50*, 11553; (k) Rabjohn, N.; Harbert, C. A. *J. Org. Chem.* **1970**, *35*, 3240; (l) Adam, S. *Tetrahedron* **1991**, *47*, 7609.
6. (a) Ouladyakhlef, A.; Boukhris, S.; Souizi, A.; Robert, A. *Bull. Soc. Chim. France* **1997**, *134*, 111; (b) Chehidi, I.; Chaabouni, M. M.; Baklouti, A. *Synth. Commun.* **1996**, *26*, 237; (c) Majcen-le Marechal, A.; Pavc, J.; Robert, A.; le Grel, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2045; (d) Babler, J. H.; Marcuccilli, C. J.; Oblong, J. E. *Synth. Commun.* **1990**, *20*, 1831.
7. The reaction and the subsequent work-up should be undertaken with care in a well ventilated hood due to the possibility of HCN liberation.
8. Characterization of 1-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-2-(piperidin-1-yl)ethane-1,2-dione (**1ad**): ^{1}H NMR (500 MHz, CD_3OD) δ 4.08 (s, 6H), 3.58 (m, 4H), 1.60 (m, 4H), 1.40 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 177.0, 174.6, 163.5, 117.7, 56.8, 48.1, 46.4, 26.8, 26.6, 25.3; HRMS *m*/*z*: $(M+H)^+$ calcd for $C_{12}H_{17}N_4O_4$: 281.1250. Found 281.1254.