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Acetonitrile Derivatives as Carbonyl Synthons. One-Pot Preparation of Diheteroaryl Ketones via a Strategy of Sequential S_NAr Substitution and Oxidation

Zhiwei Yin, Zhongxing Zhang, John F. Kadow, Nicholas A. Meanwell, and Tao Wang*

Department of Chemistry, The Bristol-Myers Squibb Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, Connecticut 06492

wangta@bms.com

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Abstract: The anion of 2-aryl acetonitrile derivatives reacted with a variety of heteroaryl chlorides or bromides in an S_NAr manifold to afford intermediate anions which were susceptible to oxidation. The addition of sodium peroxide and aqueous NH_4OAc solution effected oxidation to afford aryl heteroaryl ketones in good yields. Aryl acetonitrile derivatives are thus umpolung-type synthons of the corresponding aryl carbonyl functionality.

In a previous study, we demonstrated that N,N-disubstituted aminoacetonitrile derivatives **1** functioned as effective synthons for the corresponding amides **2**, as depicted in Figure 1A.[1,2] This reaction sequence relies upon the interception of the intermediate anion with readily available oxidants followed by release of HCN to form the carbonyl moiety, a process detailed in Scheme 1. The success of this protocol suggested that the reaction may be broadened to encompass a wider range of carbonyl derivatives if more prevalent acetonitrile reagents **3** were to participate, affording a synthon for **4**, Figure 1B.[3] Aryl heteroaryl ketones are of interest both as synthetic intermediates and as structural elements present in several drugs, including the anti-inflammatory agent ketorolac, the estrogen receptor modulator raloxifene, and the anti-arrhythmic agent amiodarone (Figure 2).[4,5]

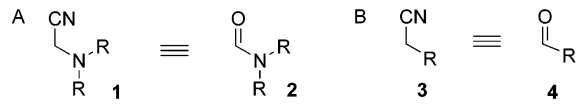


FIGURE 1. Alternative carbonyl synthons.

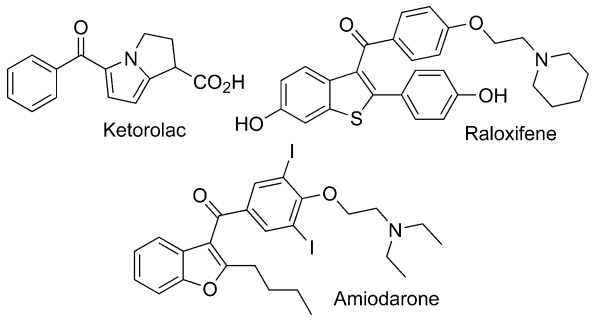
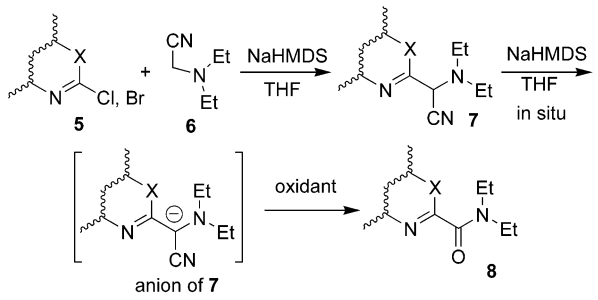


FIGURE 2. Drugs with diaryl ketone subunits.

SCHEME 1



In an attempt to identify mild conditions distinct from the traditional oxidative decyanation process mediated by base and oxygen,[3] a series of acetonitrile derivatives were exposed to a panel of solid peroxides suspended in THF at room temperature and the reactions were carefully monitored by LC−MS. Perhaps not surprisingly, the combination of structurally diverse acetonitriles and solid peroxides provided a range of outcomes. The most impressive result was obtained with 2,2-diaryl acetonitriles, which were oxidized by sodium peroxide[6] to afford the corresponding diaryl ketones predominantly. Thus, treatment of the disubstituted acetonitrile **7a** with an excess of Na_2O_2 in dry THF provided the corresponding ketone **8a** (77% yield by LC−MS analysis and 58% yield after physical isolation of the product) along with a small amount of the dimerized species **9a**.[7] In contrast, when a solution of **7a** in THF was exposed to excess of NiO_2−H_2O,[8,9] the primary product was the dimerized species **9a**, isolated in 60% yield after chromatography, as

(1) Yang, Z.; Zhang, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *Org. Lett.* **2002**, *4*, 1103.

(2) Zhang, Z.; Yin, Z.; Meanwell, N. A.; Kadow, J. F.; Wang, T. *J. Org. Chem.* **2004**, *69*, 1360.

(3) (a) Heinisch, G.; Langer, T. *J. Heterocycl. Chem.* **1993**, *30*, 1685. (b) Hermann, C. K. F.; Sachdeva, Y. P.; Wolfe, J. F. *J. Heterocycl. Chem.* **1987**, *24*, 1061. (c) Deutsch, H. M.; Shi, Q.; Gruszecka-Kowalik, E.; Schweri, M. M. *J. Med. Chem.* **1996**, *39*, 1201. (d) Haider, N.; Heinisch, G.; Moshuber, J. *Heterocycles* **1994**, *38*, 125. (e) Ohba, S.; Sakamoto, T.; Yamanaka, H. *Heterocycles* **1990**, *31*, 1301. (f) Kulp, S. S.; McGee, M. J. *J. Org. Chem.* **1983**, *48*, 4097. (g) Adam, S. *Tetrahedron* **1991**, 47, 7609.

(4) (a) Huang, Y.-C.; Majumdar, K. K.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 1682. (b) Miyashita, A.; Matsuda, H.; Suzuki, Y.; Iwamoto, K.; Higashino, T. *Chem. Pharm. Bull.* **1994**, *42*, 2017. (c) Walsh, D. A.; Moran, H. W.; Shamblee, D. A.; Welstead, W. J., Jr.; Nolan, J. C.; Sancilio, L. F.; Graff, G. *J. Med. Chem.* **1990**, *33*, 2296. (d) Krug, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1674. (e) Archer, G. A.; Kalish, R. I.; Ning, R. Y.; Sluboski, B. C.; Stempel, A.; Steppe, T. V.; Sternbach, L. H. *J. Med. Chem.* **1977**, *20*, 1312.

(5) (a) Gillis, J. C.; Brogden, R. N. *Drugs* **1997**, *53*, 139. (b) Kellen, J. A. *Curr. Drug Targets* **2001**, *2*, 423. (c) Tomaselli, G. *HeartDrug* **2001**, *1*, 183−185.

(6) (a) Holland, H. L.; Daum, U.; Riemland, E. *Tetrahedron Lett.* **1981**, *22*, 5127. (b) Ho, T.-L.; Olah, G. A. *Synthesis* **1976**, 611. (c) Vaughn, H. L.; Robbins, M. D. *J. Org. Chem.* **1975**, *40*, 1187.

(7) When α,α-diphenyl acetonitrile was used, Li_2O_2, ZnO_2, SrO_2, BaO_2, CaO_2, and MgO_2 afforded acetophenone **8h** with lower yields than Na_2O_2, while MnO_2 and NiO_2−H_2O provided a dimerized product **9h**. Oxone did not promote any reaction.

(8) (a) Sugita, J. *Nippon kagaku Zasshi* **1967**, *88*, 1235. (b) Sugita, J. *Nippon kagaku Zasshi* **1967**, *88*, 668. (c) Golding, B. T.; Hall, D. R. *J. Chem. Soc. D* **1970**, 1574. (d) Hawkins, E. G. E.; Large, R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 280.

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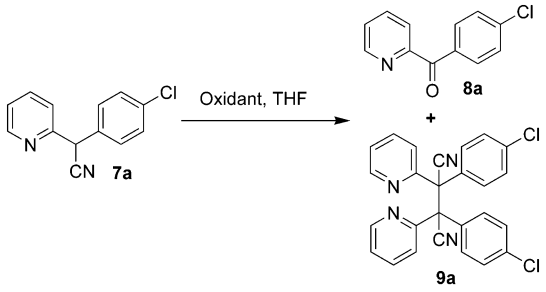
TABLE 1



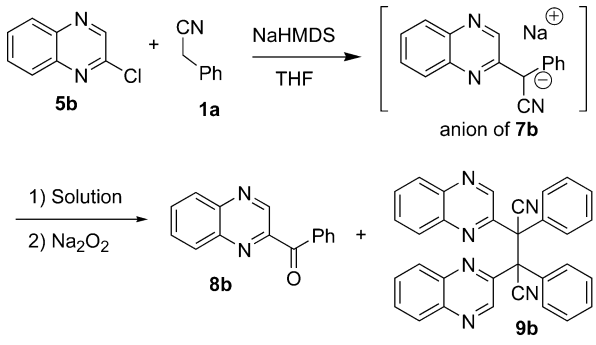
oxidant	yield of **8a** (%)	yield of **9a** (%)
NiO_2-H_2O	7	66, 60[a]
Na_2O_2	69, 58[a]	11

[a] Isolated yield; all other yields were determined by LC−MS.

depicted in the scheme associated with Table 1. Only a very minor amount of the oxidized ketone **8a** was observed under these conditions.[9] The rather clean transformation of **7a** to **8a** by simply stirring with Na_2O_2 provided mild conditions for mediating the oxidation and subsequent in situ loss of HCN[10] and established these acetonitrile derivatives as effective and convenient carbonyl synthons.[11]

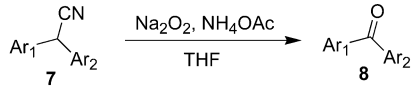
To extend the utility of this synthetic protocol, a process designed to provide aryl heteroaryl ketones by way of the reaction of heterocyclic halides with aryl acetonitrile derivatives was developed. This process relies upon the sequential S_NAr substitution of a heterocyclic halide and in situ oxidation of the product. On the basis of the electron-withdrawing properties of heterocyclic ring nitrogen atoms, it was anticipated that halogen-substituted pyridine, pyrazine, pyrimidine, pyridazine, triazine, imidazole, pyrazole, oxazole, and thiazole derivatives would react via an S_NAr process at the position α to the nitrogen atom.[3b,12] Subsequent addition of Na_2O_2 to the products in situ would then provide the desired aryl heteroaryl ketones in a protocol summarized in the scheme associated with Table 2. To establish the viability of this process, the anion of phenyl acetonitrile (**1a**), generated by treatment with a 2.5-fold excess of NaHMDS, was reacted with quinoxaline chloride **5b** in THF at room temperature to provide the intermediate anion of **7b**. In an attempt to accelerate the reaction with Na_2O_2, a saturated aqueous solution of NH_4OAc was added to the reaction mixture, conditions that provided the phenyl quinoxaline ketone **8b** in 92% yield by LC−MS and an isolated yield of 60%). Several other additives were also examined in this context, as summarized in Table 2. The majority of these conditions provided mixtures of diaryl acetonitrile **7b** and diaryl ketone **8b**, along with minor amounts of the dimerized product **9b**.

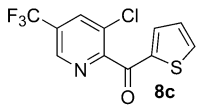
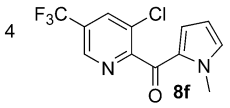
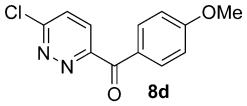
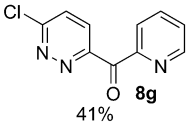
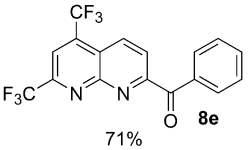
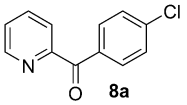
TABLE 2. Optimization of Na_2O_2 Oxidation



entry	solution in step 1	LC−MS yield (%) of **7b** after 12 h	LC−MS yield (%) of **8b** after 12 h	LC−MS yield (%) of **9b** after 12 h
1	none	36	36	4
2	water	14	76	2
3	NH_4Cl (satd)	9	77	3
4	$NaHCO_3$ (satd)	<2	88	0
5	NH_4OAc	0	92	0
6	MeOH	3.5	78	0

TABLE 3. Oxidation of Diarylacetonitrile to Diaryl Ketone by Na_2O_2



Entry	Product	Entry	Product
1	 78%[a], 72% (plus **9c** 14%)	4	 83% (plus **9f** 5%)[b]
2	 63%[a], 76% (plus **9d** 10%)	5	 41%
3	 71%	6	 69% (plus **9a** 6%)

[a] Isolated yield; all other yields were determined by LC−MS. [b] Without NH_4OAc, **8f** 64% and **9f** 27%.

Following these encouraging initial results, several commercially available disubstituted acetonitrile derivatives were exposed to Na_2O_2 and saturated NH_4OAc in THF to test the efficiency of this oxidation procedure. From the results compiled in Table 3 it is apparent that this oxidation process is both general and efficient, providing products in yields ranging from 41 to 83%, as determined by LC−MS. To further confirm the efficiency, two products were physically isolated and the yields were found to mirror those determined by LC−MS (Table 3, entries 1 and 2). Notably, this process is compatible with a range of heterocycles, including the π-excessive heterocycles thiophene and *N*-alkyl pyrrole that might be

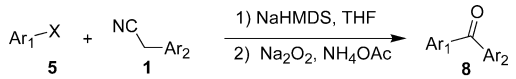
(9) Similarly, compound **7d** was treated by NiO_2-H_2O in dry THF to afford less than 5% (LC−MS) of **8d** and 76% (LC−MS)/83% (isolated) of **9d**, the dimer.

(10) Reaction and the following workup process should be undertaken cautiously in a well-ventilated hood due to the possibility of HCN liberation.

(11) (a) Larock, R. C. In *Comprehensive Organic Transformation*; Wiley-VCH: New York, 1989; p 733. (b) Hase, T. A. In *Umpoled Synthons: A Survey of Sources and Uses in Synthesis*; Wiley-Interscience: New York, 1987.

(12) Yamanaka, H.; Ohba, S. *Heterocycles* **1990**, *31*, 895.

TABLE 4. One-Pot Preparation of Phenyl Heteroaryl and Diheteroaryl Ketones via a S_NAr−Oxidation Strategy



Entry	Ar_1-X	NC-CH_2-Ar	Product	
1	**5b**	1a	**8b**	60%[a] 92%
2	**5i**	1a	**8i**	77%[a] 80% (plus **9i** 7%)
3	**5b**	1b	**8j**	70%[a] 68%
4	**5b**	1c	**8k**	74%[a] 93%
5	**5b**	1d	**8l**	48%[a] 25%
6	**5b**	1e	**8m**	62%[a] 62%
7	**5n**	1a	**8n**	42%[a] 50% (plus **9n** 12%)
8	**5o**	1a	**8o**	74%[a] 92%
9[b]	**5b**	1f	**8p**	63%
10	**5b**	1g	**8q**	75% (plus **9q** 10%)
11	**5r**	1a	**8r**	36%
12	**5s**	1a	**8s**	49%
13	**5t**	1a	**8t**	77% (plus **9t** 15%)

[a] Isolated yield; all other yields were determined by LC−MS. [b] 3.5 equiv of NaHMDS was used since the dianion of indole was assumed to be involved.

considered as substrates sensitive toward oxidation (Table 3, entries 1 and 4). Interestingly, the inclusion of NH_4OAc solution appeared to suppress the formation of dimerized product **9** (Table 1, entry 1 and Table 3, entry 6; Table 3, entry 4).

A one-pot procedure starting from heterocyclic halides (**5**) and aryl acetonitriles (**1**) was examined with a series of heterocyclic halides, a process that afforded the corresponding aryl heteroaryl ketones in yields ranging from 25 to 92%, as compiled in Table 4. Noteworthy is the compatibility of this process with heterocycles such as thiophenes that are potentially subject to oxidation and the limited formation of dimerized products.

A detailed understanding of the mechanism underlying these oxidation procedures has not been developed. The role of saturated NH_4OAc may be to facilitate dissolution of the Na_2O_2 in THF, effect protonation to produce sodium hydroperoxide and hydrogen peroxide, or a combination of both effects. However, the stability of diarylacetonitriles toward 30% H_2O_2 suggests that the latter is not the effective oxidant in this procedure.[13]

In summary, we have established mild, neutral conditions for the oxidation of aryl heteroaryl acetonitrile derivatives to the corresponding ketones. Combining this protocol with a strategy of sequential S_NAr substitution of heterocyclic halides and Na_2O_2 oxidation, a convenient one-pot process was developed that takes advantage of the umpolung nature of aryl acetonitrile derivatives as aryl carbonyl synthons. Extension of this process to encompass unactivated aromatic halides via transition metal catalysis[14] and provide diaryl ketones from aryl acetonitriles is currently under examination.

Experimental Section

General Methods. Heterocyclic halides **5** (Tables 2 and 4), acetonitriles **1** and **7** (Tables 1 and 3), and oxidative agents are commercially available and were used as received. ^1H and ^{13}C NMR spectra were obtained at 500 MHz with samples dissolved in $CDCl_3$.

General Procedures for the Preparation of Heterocyclic Diaryl Ketones As Exemplified by the Preparation of Compound 8b. NaHMDS (2.5 mL, 1.0 M in THF, 2.5 mmol)

(13) H_2O_2 (30% in water) did not oxidize diaryl acetonitriles in THF at room temperature.

(14) (a) Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330. (b) You, J.; Verkade, J. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 5051.

was added to a solution of 2-chloroquinoxaline (164 mg, 1.0 mmol) and benzyl nitrile (140 mg, 1.2 mmol) in dry THF (20 mL). After the mixture was stirred for 10 h at room temperature, saturated NH_4OAc solution (5 mL) and Na_2O_2 (340 mg, 4 mmol) was added and the mixture stirred a further 10 h at room temperature. Insoluble solids were filtered off and washed with MeOH. Concentration of the filtrate in vacuo afforded a residue which was purified by silica gel chromatography, using mixed hexane and EtOAc as eluting solvents, to provide phenylquinoxalin-2-ylmethanone **8b** (140 mg, 60%).

Acknowledgment. We thank Mr. Alan Xiang-dong Wang for valuable discussions. We are also very grateful to Dr. Li Pan for assistance in obtaining exact mass spectral data.

Supporting Information Available: ^1H and ^{13}C spectra and HRMS data of compounds **8a**−**d**,**i**−**o** and **9a**,**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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