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Cytosine Analogues from Substituted Acetonitriles via Thorpe Condensation

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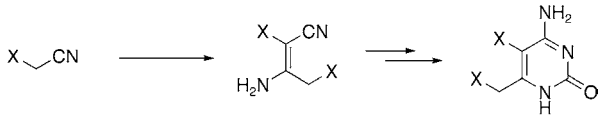
ABSTRACT



A Thorpe condensation is the key bond construction in a rapid and efficient synthesis of substituted cytosine derivatives from readily available starting materials.

Uracil and cytosine ring systems have received increasing attention due to the efficacy of anti-cancer drugs such as 5-fluorouracil and capecitabine, as well as anti-viral agents such as azidothymidine (AZT, Figure 1).[1,2] As part of our ongoing interest in heterocyclic structures, we have developed a rapid synthesis of 5-aryloxy-6-methylaryloxy-cytosines from cyanomethyl ethers via three high-yielding transformations. This report showcases the ability of the Thorpe condensation to provide an efficient route to β-enaminonitriles for the synthesis of cytosine analogues.

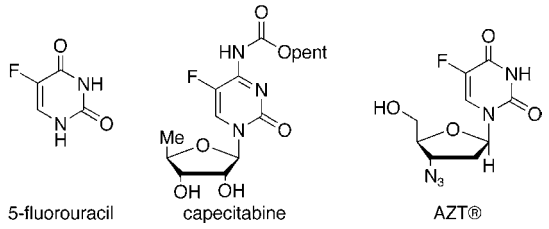


Figure 1. Representative pharmaceuticals.

During the course of our research, we noted that the treatment of a cyanomethyl aryl ether (general structure **1**)[3] with stoichiometric amounts of a potassium alkoxide base lead to high yields of a new product. Examination of the spectral data revealed that the product was an oxygenated β-enaminonitrile (general structure **2**) arising via a Thorpe condensation (see Table 1).[4] The facile intermolecular dimerization of cyanomethyl aryl ethers at low temperature was surprising, as Thorpe condensations of alkyl nitriles require elevated temperatures and prolonged reaction times.[5,6] The literature provides few examples of the Thorpe condensation of cyanomethyl ethers, and these are primarily examples of undesired side products that were isolated in poor yield.[7,8] Recognizing that β-enaminonitriles **2** could function as a scaffold for the construction of highly functionalized cytosine derivatives, we subjected a range of

(1) For an overview of nucleosides with anti-cancer activity, see: Cole, C.; Foster, A. J.; Freeman, S.; Jaffar, M.; Murray, P. E.; Stratford, I. J. *Anti-Cancer Drug Des.* **1999**, *14*, 383−392.

(2) For a review of nucleosides with anti-viral activity, see: Gumina, G.; Song, G.-Y.; Chu, C. K. *FEMS Microbiol. Lett.* **2001**, *202*, 9−15.

(3) Aryl ethers **1** were obtained in 87−99% yield from commercially available aryl alcohols (aryl alcohol, K_2CO_3, acetone, $ClCH_2CN$, reflux): (a) Benarab, A.; Boyé, S.; Savelon, L.; Guillaumet, G. *Tetrahedron Lett.* **1993**, *34*, 7567−7568. (b) Rooney, C. S.; Stuart, R. S.; Wasson, B. K.; Williams, H. W. R. *Can. J. Chem.* **1975**, *53*, 2279−2292.

(4) (a) Schaefer, J. P.; Bloomfield, J. J. *Org. React. (N. Y.)* **1967**, *15*, 1−203. (b) Davis, B. R.; Garratt, P. J. *Compr. Org. Synth.* **1991**, *2*, 848−852.

(5) Yoshizawa, K.; Toyota, S.; Toda, F. *Green Chem.* **2002**, *4*, 68−70.

(6) Cross coupling between the anion of an alkyl nitrile and a α-branched cyanomethyl ether at low temperature has been reported: Kobayashi, K.; Hiyama, T. *Tetrahedron Lett.* **1983**, *24*, 3509−3512.

(7) (a) Makosza, M.; Ziobrowski, T.; Serebriakov, M.; Kwast, A. *Tetrahedron* **1997**, *53*, 4739−4750. (b) Kovács, L. *Molecules* **2000**, *5*, 127−131.

(8) For additions of alkylmetals to cyanomethyl ethers, see: (a) Charette, A. B.; Gagnon, A. *Tetrahedron: Asymmetry* **1999**, *10*, 1961−1968. (b) Charette, A. B.; Gagnon, A.; Janes, M.; Mellon, C. *Tetrahedron Lett.* **1998**, *39*, 5147−5150. (c) Kuwahara, Y.; Yen, L. T. M.; Tominaga, Y.; Matsumoto, K.; Wada, Y. *Agric. Biol. Chem.* **1982**, *46*, 2283−2291.

10.1021/ol035223j CCC: $25.00
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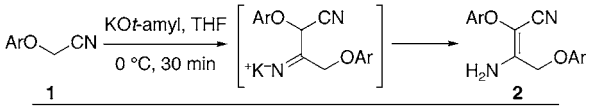
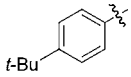
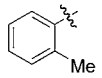
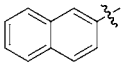
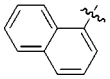
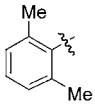
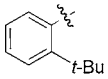
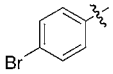
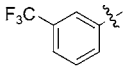
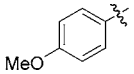
Table 1. Thorpe Condensation of Aryl Ethers



entry	#	Ar	*Z*:*E* ratio[a]	yield
1	**1a**		88:12	96%
2	**1b**		72:28	94%
3	**1c**		>95:5	99%
4	**1d**		83:17	99%
5	**1e**		>95:5	88%
6	**1f**		50:50	86%
7	**1g**		>95:5	90%
8	**1h**		>95:5	92%
9	**1i**		>95:5	89%

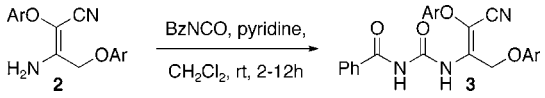
[a] Olefin isomer ratios determined by ^{1}H NMR. The structure of (*Z*)-**2d** was unambiguously assigned by fractional crystallization and single-crystal X-ray diffraction.[9] Stereochemical assignments of **2a**−**c**,**e**−**i** are provisionally assigned on the basis of analogy to **2d**.

α-aryloxyacetontriles to our reaction conditions (Table 1). These condensations afford excellent yields for a wide range of aryl ethers, including sterically hindered cases such as *ortho*-substituted aryl ethers **1b**,**d**−**f**.

The selective N-acylation of enamines **2** proved to be difficult, as mixtures of products from C and N acylation were obtained under many conditions.[10] Ultimately, treatment of enamines **2** with benzoyl isocyanate and pyridine in CH_2Cl_2 provided exclusively the desired benzoyl ureas **3** (Table 2).[11] This reaction proceeded cleanly and furnished excellent yields (88−99%).

Treatment of benzoyl ureas **3** with sodium ethoxide in refluxing ethanol cleanly removed the benzoyl group and

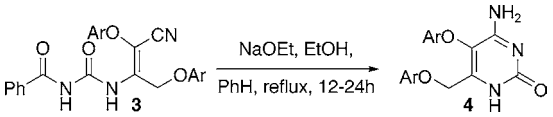
Table 2. Acylation with Benzoyl Isocyanate



entry	substrate	yield
1	**2a**	92%
2	**2b**	99%
3	**2c**	99%
4	**2d**	99%
5	**2e**	91%
6	**2f**	97%
7	**2g**	86%
8	**2h**	94%
9	**2i**	98%

induced cyclization to provide the desired cytosine analogues **4** in good to excellent yield (Table 3).[12] Although the reactions were clean and proceeded to completion, isolated yields of some analogues suffered from difficulties associated with their poor solubility. In particular, bis-*ortho*-methyl derivative **4e** is exceptionally insoluble in most solvents, which lead to a reduced isolated yield.

Table 3. Cyclization to Form Pyrimidines



entry	substrate	yield
1	**3a**	70%
2	**3b**	92%
3	**3c**	94%
4	**3d**	83%
5	**3e**	40%[a]
6	**3f**	75%
7	**3g**	69% (76%)[b]
8	**3h**	98%
9	**3i**	78%

[a] Although the NMR spectrum of the unpurified reaction showed clean and complete conversion of **3e**, isolation of **4e** was hindered by solubility problems. [b] Overall isolated yield of **4g** from **2g** without intermediate purification of **3g**.

An intramolecular variant of our procedure utilizing the bis-cyanomethyl ether **5** furnished cyclic enaminonitrile **6** (74% yield),[3b,4,13] which was transformed into benzodioxepine fused tricyclic pyrimidine **8** in good yield (67% yield for two steps, Scheme 1).

Addition of base to bromo- and chloroacetonitrile results in uncharacterizable polymeric products, while fluoroaceto-

(9) Crystallographic data for this compound has been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

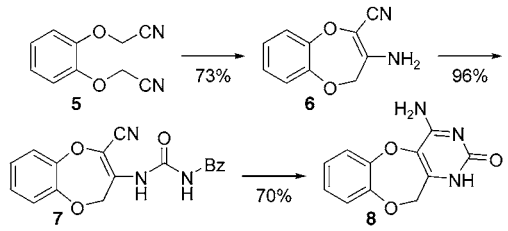
(10) Variables screened include: base (NaH, pyridine, and R_3N), solvent (THF, DMF, Et_2O, and CH_2Cl_2), and isocyanate ($ClSO_2NCO$, BnNCO, $CF_3C(O)NCO$, TMSNCO, and TsNCO).

(11) Isomer ratios of ureas **3** were unchanged from the corresponding enaminonitrile starting material.

(12) Enamines **3** must undergo *Z*/*E* isomerization to cyclize. This isomerization presumably occurs through a base-catalyzed enamine−imine tautomerization.

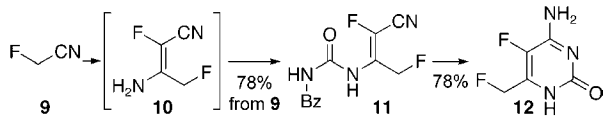
(13) For a review of the intramolecular Thorpe−Ziegler cyclization, see: Fleming, F. F.; Shook, B. C. *Tetrahedron* **2002**, *58*, 1−23.

Scheme 1



nitrile (**9**) undergoes clean dimerization to provide difluoroenamine **10**,[14] which can be converted with the aforementioned procedure into 5-fluoro-6-fluoromethylcytosine (**12**) in good yield (61% overall from **9**, Scheme 2). This is the

Scheme 2



first reported synthesis of 5-fluoro-6-fluoromethylcytosine, although the synthesis of 5-fluoro-6-fluoromethyl-uracil has been reported in poor yields using fluorine gas.[15] In contrast to the haloacetonitriles, cyanomethyl benzenesulfonate and alkyl nitriles failed to produce any dimer with our conditions and resulted in complete recovery of the starting nitrile.

In conclusion, we have developed an efficient synthesis of 5,6-disubstituted cytosine analogues using the Thorpe condensation as a key transformation. This method allows the synthesis of cytosine derivatives that are unreported in the literature and difficult to access using alternative methods. The efficiency and mild conditions of the Thorpe condensation of aryl ethers is noteworthy. Further work is underway to examine the scope and versatility of this approach for the preparation of cytosine analogues as well as to elucidate the biological activity of these interesting new analogues.

Acknowledgment. We are grateful to Brown University for research support; Dr. Tun-Li Shen for assistance with mass spectral analyses; and Dr. Joe Ziller, of the University of California, Irvine, for expert assistance with single-crystal X-ray diffraction.

Supporting Information Available: Experimental procedures and characterization for the preparation of **1a**−**i**, **2a**−**i**, **3a**−**i**, **4a**−**i**, and **5**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) It was found that dimer **10** codistills with many common organic solvents, including diethyl ether, hexanes, and ethyl acetate. Better yields of the corresponding urea were obtained when **10** was acylated directly without purification.

(15) Cech, D.; Herrmann, G.; Holy, A. *Nucleic Acids Res.* **1977**, *4*, 3259−3266.