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# A New and Facile Synthesis of Quinazoline-2,4(1*H*,3*H*)-diones

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## ABSTRACT


**A new and facile preparation of quinazoline-2,4(1*H*,3*H*)-diones was first reported which was the condensation of aromatic *o*-aminonitriles with DMF or *N*,*N*-diethylformamide in the presence of $ZnCl_2$ (0.5−10 mol %) at 190−200 °C in the sealed reactor.**

In recent decades, quinazoline-2,4(1*H*,3*H*)-diones have drawn the attention of chemists and medicinal chemists because of their various biological activities for use as α-adrenergic receptor antagonists,[1] anticonvulsants,[2] antibacterial,[3] psychosedative,[4] antihypertensive,[5] or hypotensive compounds, or inhibitors of puromycin-sensitive aminopeptidase.[6] Quinazoline-2,4(1*H*,3*H*)-diones are also useful synthetic materials in heterocyclic chemistry.[7] There are a number of synthetic methods available for the preparation of quinazoline-2,4(1*H*,3*H*)-diones. *o*-Amino-benzoic acid or its derivatives,[8] *o*-aminobenzonitrile,[9] isatoic anhydride,[10] *o*-azidobenzoic acid,[11] halobenzoic acid and its ester,[12] 2-carbomethoxyphenyl isocyanate,[13] *N*-arylnitrilium salts,[14] and 4*H*-3,1-benzoxazinone[15] are common starting materials for their preparation. Some environmental benign methods such as solid-phase synthesis are also used for preparation of quinazoline-2,4(1*H*,3*H*)-diones.[16] Recently, Mizuno, et al.[17] described a

(1) (a) Connolly, T. J.; Keitz, P. F.; Lee, E. K.; Li, J.; Lopez-Tapia, F. J.; McGarry, P. F.; Melville, C. R.; Nitzan, D.; O'Yang, C.; Padilla, F.; Weinhardt, K. K. PCT Int. Appl. WO 2005005395 A2 20050120, 2005. (b) Miyata, T.; Mizuno, T.; Nagahama, Y.; Nishiguchi, I.; Hirashima, T.; Sonoda, N. *Heteroatom Chem.* **1991**, *2*, 473. (c) Tran, T. P.; Ellsworth, E. L.; Stier, M. A.; Domagala, J. M.; Showalter, H. D. H.; Gracheck, S. J.; Shapiro, M. A.; Joannides, T. E.; Singh, R. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4403.

(2) Hayao, S.; Havera, H. J.; Strycker, W. G.; Leipzig, T. J.; Kulp, R. A.; Hartzler, H. E. *J. Med. Chem.* **1965**, *8*, 807.

(3) (a) Kakuta, H.; Tanatani, A.; Nagasawa, K.; Hashimoto, Y. *Chem. Pharm. Bull.* **2003**, *51*, 1273. (b) Boyles, D. C.; Curran, T. T.; Parlett, R. V., IV. *Org. Process Res. Dev.* **2002**, *6*, 230.

(4) Meuldermans, W.; Hendrickx, J.; Woestenborghs, R.; van Peer, A.; Lauwers, W.; De Cree, J.; Heykants, J. *Arzneim.-Forsch.* **1988**, *38*, 789.

(5) (a) Imagawa, J.; Sakai, K. *J. Pharmacol.* **1986**, *131*, 257. (b) Russell, R. K.; Press, J. B.; Rampulla, R. A.; McNally, J. J.; Falotico, R.; Keiser, J. A.; Bright, D. A.; Tobia, A. *J. Med. Chem.* **1988**, *31*, 1786. (c) Russo, F.; Romeo, G.; Guccione, S.; De Blasi, A. *J. Med. Chem.* **1991**, *34*, 1850.

(6) (a) Mounetou, E.; Legault, J.; Lacroix, J.; C-Gaudreault, R. *J. Med. Chem.* **2001**, *44*, 694. (b) Chao, Q.; Deng, L.; Shih, H.; Leoni, L. M.; Genini, D.; Carson, D. A.; Cottam, H. B. *J. Med. Chem.* **1999**, *42*, 3860.

(7) (a) Peet, N. P.; Anzeveno, P. B. *J. Heterocycl. Chem.* **1979**, *16*, 877. (b) Michel, J.; Toulmě, J. J.; Vercauteren, J.; Moreau, S. *Nucleic, Acids Res.* **1996**, *24*, 1127. (c) Fujino, K.; Takami, H.; Atsumi, T.; Ogasa, T.; Mohri, S.; Kasai, M. *Org. Process Res. Dev.* **2001**, *5*, 426. (d) Andrus, M. B.; Mettath, S. N.; Song, C. *J. Org. Chem.* **2002**, *67*, 8284.

(8) (a) Petrov, J. S.; Andreev, G. N. J. *Org. Process Res. Dev.* **2005**, *37*, 560. (b) Li, Z.; Huang, H.; Sun, H.; Jiang, H.; Liu, H. *J. Comb. Chem.* **2008**, *10*, 484. (c) Kornet, M. J. *J. Comb. Chem.* **2008**, *10*, 1533. (d) Couture, A.; Cornet, H.; Grandclaudon, P. *Synthesis* **1991**, 1009.

(9) (a) Taylor, E. C.; Shvo, Y. *J. Org. Chem.* **1968**, *33*, 1719. (b) Papadopoulos, E. P. *J. Heterocycl. Chem.* **1981**, *18*, 515. (c) Papadopoulos, E. P. *J. Heterocycl. Chem.* **1980**, *17*, 1553. (d) Mizuno, T.; Okamoto, T.; Ito, T.; Miyata, T. *Tetrahedron Lett.* **2000**, *41*, 1051. (e) Mizuno, T.; Ishino, Y. *Tetrahedron* **2002**, *58*, 3155.

(10) Minami, T.; Ogata, M.; Hirao, I. *Synthesis* **1982**, 231.

(11) Molina, P.; Alajarin, M.; Vidal, A. *Heterocycles* **1989**, *45*, 4263.

(12) (a) Tran, T. P.; Ellsworth, E. L.; Watson, B. M.; Sanchez, J. P.; Showalter, H. D. H.; Rubin, J. R.; Stier, M. A.; Yip, J. Y.; Nguyen, D. Q.; Bird, P.; Singh, R. *J. Heterocycl. Chem.* **2005**, *42*, 669. (b) Willis, M. C.; Snell, R. H.; Fletcher, A. J.; Woodward, R. L. *Org. Lett.* **2006**, *8*, 5089.

(13) Canonne, P.; Aksssira, M.; Dahdouh, A.; Kasmi, H.; Boumzebra, M. *Heterocycles* **1993**, *36*, 1305.

(14) Al-Talib, M.; Jochims, J. C.; Hamed, A.; Gafg, Q.; Ismail, A. E. *Synthesis* **1992**, 697.

(15) (a) Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12. (b) Doleschall, G.; Lempert, K. J. *Monatsh. Chem.* **1964**, *95*, 1068.

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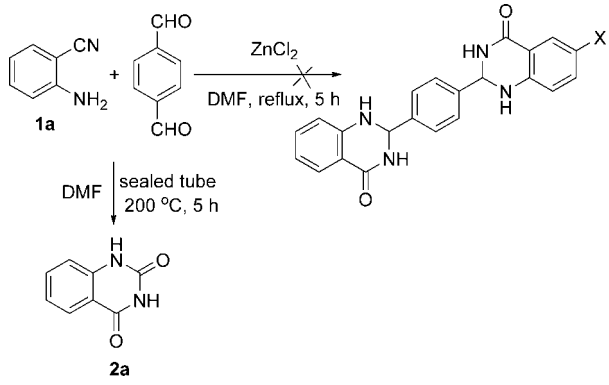
convenient synthesis of quinazoline-2,4(1*H*,3*H*)-diones from 2-aminobenzonitriles by the chemical fixation of carbon dioxide in the presence or absence of base using DMF as a solvent. Later, they[18] also reported a simple solvent-free modified synthesis of quinazoline-2,4(1*H*,3*H*)-diones from 2-aminobenzonitriles in the presence of catalytic amount of base under supercritical $CO_2$ conditions. Here, supercritical $CO_2$ conditions acted as both a reactant and a solvent. However, some drawbacks present in these methods include multistep procedures, toxic reagents, time-consuming experimental procedures, and environmental impact. Therefore, a new facile and effective method for synthesis of quinazoline-2,4(1*H*,3*H*)-diones is urgently needed.

In our previous research of cyclocondensation of aromatic *o*-aminonitriles with ketones under the catalysis of $ZnCl_2$, a new conversion to form 1,2-dihydroquinazoline-4(3*H*)-one derivatives was found coexisting with the normal Friedländer-type quinoline annulation.[19] Thus, we thought similar 1,2-dihydroquinazoline-4(3*H*)-ones could be afforded by the reaction of *o*-aminonitriles with aromatic aldehydes through this conversion. To our surprise, the reaction of 2-aminobenzonitrile **1a** with terephthalaldehyde in the sealed reactor under the catalyst of $ZnCl_2$ (0.1 mol %) at 200 °C afforded a white product instead of the expected symmetrical bis-dihydroquinazolin-4(3*H*)-one (Scheme 1), and this product

**Scheme 1.** Reaction of *o*-Aminobenzonitrile with Terephthalaldehyde




was characterized as quinazoline-2,4(1*H*,3*H*)-dione on the basis of its spectra and analytical data. Moreover, its structure was further confirmed by X-ray crystallographic diffraction (Figure 1) and compared with the authentic sample.

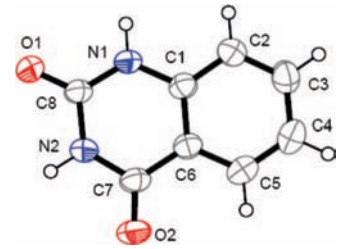
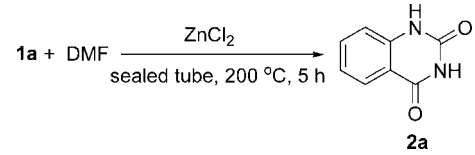



**Figure 1.** Crystal structure of compound **2a**.

In fact, the reactant, terephthalaldehyde, could be competely recovered from the reaction mixture. Thus, we speculated DMF was involved in the reaction. To our delight, **2a** was obtained as the only product with the same reaction in the absence of terephthalaldehyde (Scheme 1).

To obtain the optimal reaction conditions, a variety of catalysts were first investigated for detecting the catalytic activities of different metal ions for the product of **2a** (Table 1). The data indicated that $ZnCl_2$ is the most effective (Table

**Table 1.** Effect of Catalyts for Synthesis of **2a**[a]




| entry | conditions | yield[b] (%) |
|---|---|---|
| 1 | $ZnCl_2$ (1 equiv) | 23 |
| 2 | $CuCl_2$ (1 equiv) | 20 |
| 3 | $HgCl_2$ (1 equiv) | 15 |
| 4 | $FeCl_3$ (1 equiv) | 0 |
| 5 | $AlCl_3$ (1 equiv) | 0 |
| 6 | $SnCl_2$ (1 equiv) | 0 |
| 7 | $TiCl_4$ (1 equiv) | 2 |
| 8 | $ZnCl_2$ (0.5 equiv) | 14 |
| 9 | $ZnCl_2$ (2 equiv) | 62 |
| 10 | $ZnCl_2$ (5 equiv) | 90 |
| 11 | $ZnCl_2$ (10 equiv) | 89 |
| 12 | $ZnCl_2$ (5 equiv, <190 °C) | No product |
| 13 | $ZnCl_2$ (5 equiv, 2 h) | 54 |
| 14 | $ZnCl_2$ (5 equiv, 4 h) | 82 |
| 15 | $ZnCl_2$ (5 equiv, 5 h) | 90 |

[a] Reactions were carried out in DMF at 200 °C. [b] Isolated yield.

1, entries 1 and 8−11). $CuCl_2$ and $HgCl_2$ also promoted the reaction successfully, but the yields of **2a** are lower, 20% and 15%, respectively (Table 1, entries 2 and 3). Other catalysts, including $AlCl_3$, $FeCl_3$, etc., failed to afford compound **2a** (Table 1, entries 4−7). We further found that the best yield of compound **2a** was obtained when 5 equiv of $ZnCl_2$ was used (Table 1, entry 10). The excessive amount of $ZnCl_2$ for this annulation is probably due to the chelating effect of zinc ion. After screening the effect of reaction time and temperature

(16) (a) Gouilleux, L.; Fehrentz, J.-A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7031. (b) Buckman, B. O.; Mohan, R. *Tetrahedron Lett.* **1964**, *5*, 4439. (c) Connolly, T. J.; McMarry, P.; Sukhtankar, S. *Green Chem.* **2005**, *7*, 586. (c) Mizuno, T.; Ishino, Y. *Tetrahedron* **2002**, *58*, 3455. (d) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073.

(17) (a) Mizuno, T.; Okamoto, N.; Ito, T.; Miyata, T. *Tetrahedron Lett.* **2000**, *41*, 1051. (b) Mizuno, T.; Okamoto, N.; Ito, T.; Miyata, T. *Heteroaom. Chem.* **2000**, *11*, 428. (c) Mizuno, T.; Ishino, Y. *Tetrahedron* **2002**, *58*, 3155.

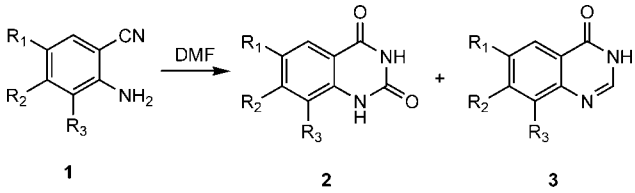
(18) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073.

(19) Li, J. R.; Zhang, L. J.; Shi, D. X.; Li, Q.; Wang, D.; Wang, C. X.; Zhang, Q.; Zhang, L.; Fan, Y. Q. *Synlett* **2008**, 233.

(Table 1, entries 12−15), the appropriate yield was achieved with the reaction conditions of **1a** with DMF at 190−200 °C for 5 h.

With the optimized reaction conditions in hand, various *o*-aminobenzonitriles **1** were utilized to react with DMF, and the reaction results are listed in Table 2. As shown in Table 2, the *o*-aminobenzonitriles **1** possessing electron-donating or -accepting substituted groups on the aromatic ring were readily reacted with DMF to yield the corresponding quinazoline-2,4(1*H*,3*H*)-diones in the range, and reactions *o*-aminobenzonitriles with electron-donating groups proceeded smoothly to afford the desired compounds in comparatively good yields (Table 2, entry 2). *o*-Electron-deficient *o*-aminobenzonitriles, such as Cl, Br, or $NO_2$ derivarives, afforded quinazoline-2,4(1*H*,3*H*)-diones in moderate yields. This was because of a competitive formation of quinazoline-4(1*H*)-one as a byproduct (Table 2, entries 4−7). But 5-iodo-2-aminobenzonitrile gave in good yield compound **2c** (Table 2, entry 3), and 8-bromo-6-nitro-quinazoline-4(3*H*)-one was obtained in an isolated yield of 31% as the only product by condensation of 3-bromo-5-nitro-2-aminobenzonitrile with DMF (Table 2, entry 8).

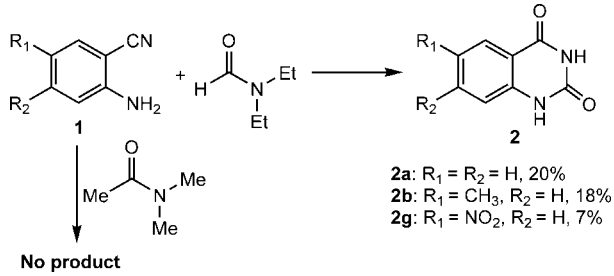
**Table 2.** Synthesis of Substituted Quinazolin-2,4(1*H*,3*H*)-diones[a]




| entry | $R_1$ | $R_2$ | $R_3$ | yield of **2** (%)[b] | yield of **3** (%)[b] |
|---|---|---|---|---|---|
| 1 | H | H | H | 90 (**2a**) | |
| 2 | $CH_3$ | H | H | 91 (**2b**) | |
| 3 | I | H | H | 80 (**2c**) | |
| 4 | Cl | H | H | 37 (**2d**) | 37 (**3d**) |
| 5 | H | Cl | H | 36 (**2e**) | 35 (**3e**) |
| 6 | Br | H | H | 41 (**2f**) | 39 (**3f**) |
| 7 | $NO_2$ | H | H | 24 (**2g**) | 22 (**3g**) |
| 8 | $NO_2$ | H | Br | | 31 (**3h**) |

[a] All reactions were carried out using catalyst (5 equiv). [b] Isolated yield.

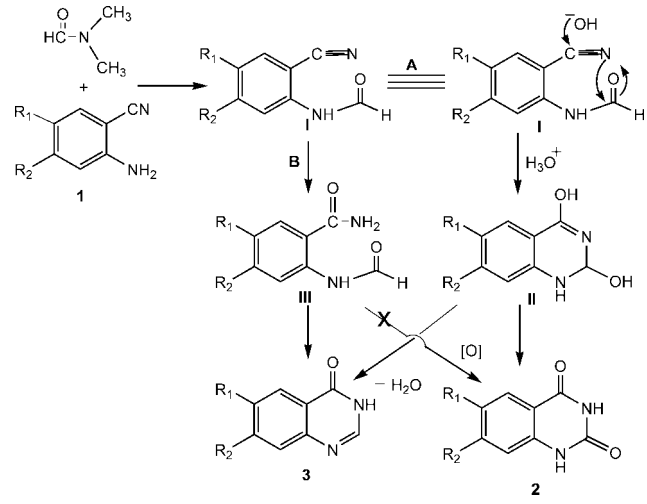
**Scheme 2.** Reaction of *o*-Aminobenzonitriles with *N*,*N*-Diethylformamide



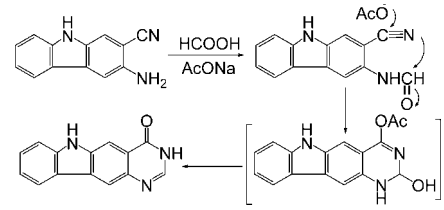

For the investigation of the reaction mechanism, replacement of DMF with *N*,*N*-diethylformamide afforded **2a**,**b**,**g** at relatively low yields, but no reaction was observed when DMF was replaced by *N*,*N*-dimethylacetamide (Scheme 2), so the formyl proton is necessary.

On the basis of the above-mentioned results, a possible reaction mechanism was shown in Scheme 3. The formylation of *o*-aminobenzonitrile by DMF gave intermediate **I**, followed the two different routes: (A) intramolecular cyclization of **I** to form the hydroxy intermediate **II**, and then oxidization to produce quinazolinedione **2** or dehydration to form compound **3**; (B) hydration of **I** into a benzamide **III** followed by intramolecular cyclization of **III** afforded **3**. Thus, route A is reasonable. Further evidence is that the reaction of 2-aminobenzamide with DMF under the standard conditions only afforded quinazolinone, and no product was detected by the reaction of **1a** with DMF in hydrochloride solution. In addition, this proposed mechanism was also confirmed by the literature,[20,21] and quinazolinones were provided by the cyclization of *o*-amidobenzamides.[22]

**Scheme 3.** Possible Reaction Mechanism




(20) The cyclization of aromatic *o*-aminonitrile with formic acid under sodium acetate gave quinazolinone through a similar intermediate; see: Gazengel, J. M.; Lancelot, J. C.; Rault, S.; Robba, M. *J. Heterocycl. Chem.* **1989**, *26*, 1135–1139.




(21) One relative patent has mentioned that the reaction of 2-aminobenzonitrile with DMF was performed in two steps of which one is base catalyzed and the other is acid (HCl/water) catalyzed. See: Kawano, N.; Ishikawa, N.; Kaizawa, H.; Masuda, N.; Hamaguchi, W.; Koganemaru, Y.; Kato, K.; Miyazaki, T. PCT Int. Appl. WO 2005123697 A1 20051229, 2005.

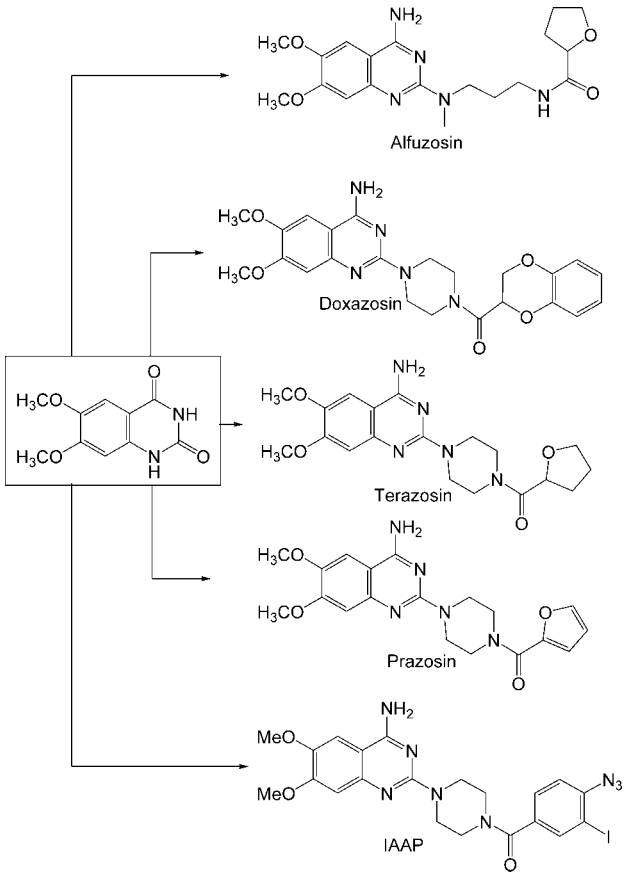
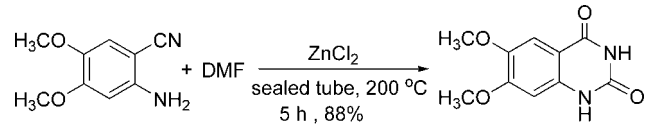



**Figure 2.** 6,7-Dimethoxyquinazoline-2,4(1*H*,3*H*)-dione is a key intermediate of alfuzosin, prazosin, terazosin, doxazosin, and IAAP.

It is worth emphasizing that 6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione is a key intermediate for production of medicines such as alfuzosin, prazosin, terazosin, doxazosin, and IAAP (Figure 2).[23] These drugs, which are effective $\alpha_1$-adrenergic blockers, are useful for antihypertensives. Traditionally, 6,7-dimethoxyquinazoline-2,4(1*H*,3*H*)-dione is obtained from the cyclization of 2-amino-4,5-dimethoxybenzoic acid with toxic sodium cyanate in acetic acid.[24] The condensation of commercially available 2-amino-4,5-dimethoxybenzonitrile with DMF under the catalysis of $ZnCl_2$ in a sealed reactor gave the target compound in 88% yield (Scheme 4), thereby avoiding highly toxic sodium cyanate.

**Scheme 4.** Synthesis of 6,7-Dimethoxyquinazoline-2,4(1*H*,3*H*)-dione




In summary, a facile method for the synthesis of quinazoline-2,4(1*H*,3*H*)-diones was provided. This new procedure avoids the use of toxic reagent, and the workup is very convenient. Extension of this new synthetic methodology and a detailed investigation of its mechanism are currently in progress.

**Acknowledgment.** Support from the Beijing Institute of Technology is gratefully acknowledged. We are also grateful to Analysis Centers of Peking University and Institute of Chemistry, Chinese Academy of Sciences for element analysis, MS, and NMR detection.

**Note Added after ASAP Publication.** There were errors in the description of the mechanism of Scheme 3 in the version published ASAP February 24, 2009; the corrected version published on the web March 12, 2009.

**Supporting Information Available:** Experimental procedures and full characterization for some compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Zentmyer, D. T.; Wanger, E. C. *J. Org. Chem.* **1949**, *14*, 967–981.

(23) (a) Manoury, P. M. *J. Med. Chem.* **1986**, *29*, 19–25. (b) Bunin, B. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1981**, *95*, 6225b. (c) Chadwick, D. J.; McKnight, M. V.; Ngochindo, R. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1343–1347. (d) Campbell, S. F.; Davey, M. J.; Hardstone, J. D.; Lewis, J. D.; Lewis, B. N.; Palmer, M. J. *J. Med. Chem.* **1987**, *30*, 49–57. (e) Andrus, M. B.; Mettath, S. N.; Song, C. *J. Org. Chem.* **2002**, *67* (23), 8284–8286.

(24) (a) Lange, N. A.; Sheibley, F. E. *Org. Synth* **1943**, *2*, 79–80. (b) Andrus, M. B.; Mettath, S. N.; Song, C. *J. Org. Chem.* **2002**, *67*, 8284–8286.