Communication

TBAF-Mediated Dimerization Reaction of β,γ-Unsaturated Arylketones

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A simple and high-yield method for the synthesis of several 1,5-diaryl-1,5-dicarbonyl compounds has been established starting from TBAF-mediated isomerization and dimerization reaction of β,γ-unsaturated arylketones (allyl arylketones) with mono-, di-, and tri-methoxy groups, which is derived from allylation of commercially available different benzaldehydes and followed by oxidation of the resulting secondary alcohols.

Keywords: TBAF; Dimerization; β,γ-Unsaturated arylketones.

INTRODUCTION

Among the fluoride ion sources, tetra-*n*-butylammonium fluoride (TBAF) is the most popular candidate for various synthetic proposes. The fluoride anion could be an efficacious basic activator in different reactions. Accordingly, some new and efficient fluoride-promoted methods warrant attention.[1,2] Recently, DeShong and co-worker demonstrated the superiority of tetra-*n*-butylammonium triphenyldifluorosilicate (TBAT) over TBAF as a fluoride source for various reactions.[3a,b] Fry and coworker have also reported that the dimerization reaction of methyl crotonate by TBAT afforded a 7:1 *E*/*Z* mixture in 74% yield at reflux temperature for 4 h under a nitrogen system.[3c] The proposed mechanism has been studied well. Although TBAT was a more efficient reagent than TBAF in different reactions, the commercially available TBAF is still more convenient and cheaper than freshly prepared TBAT.

In order to reinvestigate this dimerization reaction, TBAF was chosen as the starting fluoride ion source. With the related dimerization literature reports of α,β-unsaturated esters by different initiators (e.g. metal ion complex, trialkylphosphine, tetra-alkylammonium cyanide, TBAT) in hand,[3c,4] we tried to examine the TBAF-mediated dimerization reaction of methyl crotonate and methyl cinnamate (β-methyl and β-phenyl vinylesters). However, the desired dimers were obtained in trace yields.

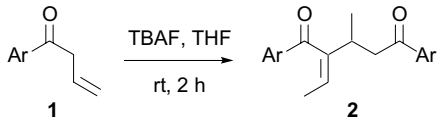
RESULTS AND DISCUSSION

To improve the yield and reactivity of the TBAF-mediated dimerization reaction of α,β-unsaturated compounds, we turned to the examination of vinylketones. After treatment of vinylketones with α′-aliphatic groups (methyl and benzyl) and α′-aromatic groups (phenyl and 3,4-dimethoxyphenyl) by TBAF, the starting material was recycled as the major product.

For exploring a more applicable substrate toward the TBAF-mediated dimerization reaction, we found that allylketone with 4-methoxyphenyl group was the better substrate, and the resultant sole *Z*-isomer was obtained in 93% yield at rt for 2 h without an atmosphere of nitrogen and dry solvent system. During the course of our investigation, these dimerization reactions of other allylketones with aromatic substitutents (e.g. phenyl, 4-fluorophenyl-, 2-furanyl, 2-pyridinyl, 2-indolyl and 2-quinolinyl) with TBAF were unsuccessful under different conditions. The difference between α,β-unsaturated arylketone and β,γ-unsaturated arylketone was not further investigated.

Although the dimerization process of α,β-unsaturated ester has been developed by Fry's group, the present work toward TBAF-mediated dimerization reaction of β,γ-unsaturated arylketone is complementary to existing methodology. As shown in Table 1, it became apparent that many substituted 1,5-dicarbonyl compounds having 1,5-

Table 1. TBAF-mediated dimerization of ketones **1a**-**k** and the good yields of the *Z*-isomers **2a**-**k**[a]

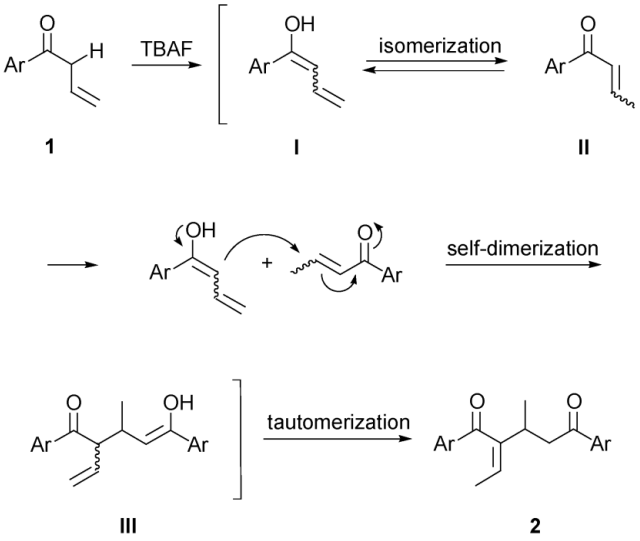


1 **2**

Entry	**1**, Ar	**2**, Yield[a]
1	**1a**, 2-$CH_3OC_6H_4$	**2a**, 90%
2	**1b**, 3-$CH_3OC_6H_4$	**2b**, 94%
3	**1c**, 4-$CH_3OC_6H_4$	**2c**, 93%
4	**1d**, 3,4-$CH_2O_2C_6H_3$	**2d**, 95%
5	**1e**, 3,4-$(CH_3O)_2C_6H_3$	**2e**, 95%
6	**1f**, 3-C_4H_9O-4-$CH_3OC_6H_3$	**2f**, 94%
7	**1g**, 3-$C_{10}H_{21}O$-4-$CH_3OC_6H_3$	**2g**, 89%
8	**1h**, 3-$CH{=}CH_2CH_2O$-4-$CH_3OC_6H_3$	**2h**, 93%
9	**1i**, 3-$C_6H_5CH_2O$-4-$CH_3OC_6H_3$	**2i**, 92%
10	**1j**, 3,4,5-$(CH_3O)_3C_6H_2$	**2j**, 94%
11	**1k**, 3-F-4-$OCH_3C_6H_3$	**2k**, 90%

[a] The yields of compounds **2a**-**k** was adjusted based on isolated products.

Scheme I The proposed dimerization mechanism of aryl allylketones **1a**-**k** with TBAF



diaryl substitutents with a methoxy donating group required by us could not be obtained in satisfactory yields following reported methods.

Herein, we report a simple and high-yield method toward 1,5-dicarbonyl compounds **2a**-**k** via TBAF-mediated dimerization reaction of different β,γ-unsaturated arylketones **1a**-**k** with mono-, di- and tri-methoxy groups. These experimental results are summarized in Table 1.[5] In view of the experimental simplicity, the yield of compound **2a** (3.24 g, 90%) was also provided in a multigram scale from compound **1a** (1.8 g, 10 mmole).

How are *Z*-form dimers **2a**-**k** generated under the TBAF-mediated dimerization condition? Mechanically it is not clear if the reaction follows the same pathway (Scheme I).[3c] The most likely explanation would be that isomerization of compounds **1a**-**k** is controlled by involvement of the fluoride ion to form the equilibrium of intermediates **I** and **II**. Because of the weaker basicity of fluoride ion and the presence of starting ketone as a proton source, the overall event may be considered to yield intermediate **III** via the self-dimerization of the intermediate **I** and **II** and followed by tautomerization. By a series of prototropic shifts, the more stable *Z*-form dimers **2a**-**k** can be generated as the sole product.

During the specific dimerization process, the other possible isomer analogs were not observed. For generating the sole *Z*-isomer, the major reason should be the repulsion force between the two methyl groups under thermodynamic equilibration. In comparison with a related literature report,[3c] the structural assignment of vinyl β-proton quartets was made as the *Z*-isomer (q, δ 5.90~6.20). It is worthy of note that 1,5-dicarbonyl compounds **2a**-**k** could be useful building blocks in the search for various multi-substituted pyridines with different applications.[6] Dimers **2a**-**k** with an α,β-unsaturated system could be applied in the preparation of the related analogs with potential biological activities.[7]

In summary, we have developed a simple and high-yield approach toward the 1,5-diaryl-1,5-diketone derivatives via the dimerization of β,γ-unsaturated arylketones with TBAF. Further novel TBAF-mediated methodologies and related applications are now underway.

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REFERENCES AND NOTES

1. Crouch, R. D. *Tetrahedron* **2004**, *60*, 5833.
2. (a) Amantini, D.; Beleggia, R.; Frenguelli, F.; Pizzo, F.;

Vaccaro, L. *J. Org. Chem.* **2004**, *69*, 2896. (b) Nakamura, H.; Aoyagi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1167. (c) Kuduk, S. D.; DiPardo, R. M.; Bock, M. G. *Org. Lett.* **2005**, *7*, 577. (d) Seganish, W. M.; Mowery, M. E.; Riggleman, S.; DeShong, P. *Tetrahedron* **2005**, *61*, 2117. (e) Kang, S. K.; Kim, T. H.; Pyun, S. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 797. (f) Heuft, M. A.; Collins, S. K.; Yap, G. P. A.; Fallis, A. G. *Org. Lett.* **2001**, *3*, 2883.

3. (a) Pilcher, A. S.; Ammon, H. L.; DeShong, P. *J. Am. Chem. Soc.* **1995**, *117*, 5166. (b) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901. (c) Xuan, J. X.; Fry, A. J. *Tetrahedron Lett.* **2001**, *21*, 3275.
4. (a) Saegusa, T.; Ito, Y.; Tomita, S.; Kinoshita, H. *J. Org. Chem.* **1970**, *35*, 670. (b) White, D. A.; Baizer, M. M. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2230. (c) Ikeda, M.; Hirano, T.; Tsuruta, T. *Tetrahedron* **1974**, *30*, 2217. (d) Shabtai, J.; Ney-Igner, E. *J. Org. Chem.* **1981**, *46*, 3795. (e) Chuit, C.; Corriu, R. J. P.; Reye, C. *Synthesis* **1983**, 294. (f) Komiya, S.; Oyasato, N.; Furukawa, T. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 4078.
5. TBAF-mediated dimerization of β,γ-unsaturated arylketones **1a-k** into 1,5-diaryl-1,5-diketones **2a-k** is as follows: A solution of tetra-*n*-butylammonium fluoride (1.0 M in tetrahydrofuran, 0.52 mL, 0.52 mmol) in tetrahydrofuran (2 mL) was added to a solution of β,γ-unsaturated arylketones **1a-k** (0.5 mmol) in tetrahydrofuran (5 mL) at rt. The reaction mixture was stirred at rt for 2 h, poured into aqueous ammonium chloride solution (15%, 2 mL), and concentrated. The residue was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/ethyl acetate = 8/1~10/1) afforded compounds **2a-k**. Representative data for compound **2a**: HRMS (ESI) *m*/*z* calcd for $C_{22}H_{25}O_4$ (M^++1) 353.1753, found 353.1755; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 2.0, 7.5 Hz, 1H), 7.42 (ddd, *J* = 2.0, 7.5, 9.0 Hz, 1H), 7.33 (ddd, *J* = 2.0, 7.5, 9.0 Hz, 1H), 7.12 (dd, *J* = 2.0, 7.5 Hz, 1H), 6.97 (dt, *J* = 1.0, 7.5 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.91 (dd, *J* = 1.0, 7.5 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.20 (q, *J* = 7.0 Hz, 1H), 3.88 (s, 3H), 3.72 (s, 3H), 3.62-3.53 (m, 2H), 3.38-3.31 (m, 1H), 1.89 (d, *J* = 7.0 Hz, 3H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.64, 198.73, 158.29, 156.85, 146.37, 142.92, 132.90, 130.62, 130.55, 129.92, 129.12, 128.96, 120.42, 119.99, 111.49, 111.22, 55.55, 55.46, 48.08, 28.53, 19.18, 14.46. For compound **2b**: HRMS (ESI) *m*/*z* calcd for $C_{22}H_{25}O_4$ (M^++1) 353.1753, found 353.1757; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 2.0, 2.5 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.19-7.17 (m, 2H), 7.07 (dd, *J* = 2.5, 8.5 Hz, 1H), 7.02 (dd, *J* = 2.5, 8.5 Hz, 1H), 6.20 (q, *J* = 7.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.61-3.54 (m, 1H), 3.54 (dd, *J* = 7.0, 17.0 Hz, 1H), 3.30 (dd, *J* = 6.5, 17.0 Hz, 1H), 1.94 (d, *J* = 7.0 Hz, 3H), 1.33 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.77, 199.10, 159.72, 159.28, 144.32, 140.71, 139.92, 138.57, 129.47, 128.91, 122.25, 120.85, 119.54, 117.98, 113.87, 112.08, 55.36, 55.32, 43.42, 29.25, 19.37, 14.06. For compound **2c**: HRMS (ESI) *m*/*z* calcd for $C_{22}H_{25}O_4$ (M^++1) 353.1753, found 353.1756; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.07 (q, *J* = 7.0 Hz, 1H), 3.85 (s, 6H), 3.61-3.54 (m, 1H), 3.42 (dd, *J* = 7.5, 17.0 Hz, 1H), 3.26 (dd, *J* = 7.0, 17.0 Hz, 1H), 1.92 (d, *J* = 7.0 Hz, 3H), 1,30 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.62, 198.37, 163.32, 162.71, 144.37, 136.95 (2x), 132.00 (2x), 131.79, 130.41 (2x), 113.57 (2x), 113.24 (2x), 55.40, 55.39, 43.04, 29.55, 19.47, 13.83. For compound **2d**: HRMS (ESI) *m*/*z* calcd for $C_{22}H_{21}O_6$ (M^++1) 381.1338, found 381.1337; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.42 (d, *J* = 1.5 Hz, 1H), 7.26 (dd, *J* = 1.5, 8.0 Hz, 1H), 7.20 (d, *J* = 1.5 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 6.07 (q, *J* = 7.0 Hz, 1H), 6.00 (s, 4H), 3.57-3.50 (m, 1H), 3.38 (dd, *J* = 7.5, 17.0 Hz, 1H), 3.19 (dd, *J* = 6.5, 17.0 Hz, 1H), 1.91 (d, *J* = 7.0 Hz, 3H), 1.27 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.96, 197.72, 151.55, 150.92, 148.02, 147.55, 144.13, 137.12, 133.48, 132.13, 126.04, 124.46, 109.54, 107.81, 107.72, 107.43, 101.70, 101.61, 43.07, 29.52, 19.41, 13.81. For compound **2f**: HRMS (ESI) *m*/*z* calcd for $C_{30}H_{41}O_6$ (M^++1) 497.2903, found 497.2902; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.51 (d, *J* = 1.5 Hz, 1H), 7.32 (d, *J* = 2.0 Hz, 1H), 7.26 (dd, *J* = 1.5, 8.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.07 (q, *J* = 7.0 Hz, 1H), 4.08-4.02 (m, 4H), 3.90 (s, 6H), 3.61-3.54 (m, 1H), 3.44 (dd, *J* = 7.5, 17.0 Hz, 1H), 3.21 (dd, *J* = 6.5, 17.0 Hz, 1H), 1.92 (d, *J* = 7.0 Hz, 3H), 1.86-1.80 (m, 4H), 1.53-1.45 (m, 4H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.98 (t, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.76, 198.47, 153.48, 152.87, 148.40, 148.20, 144.14, 136.71, 131.74, 130.45, 124.58, 122.80, 113.10, 111.47, 110.14, 109.77, 68.65, 68.62, 56.01 (2x), 42.94, 31.11, 31.07, 29.74, 19.54, 19.16 (2x), 13.85, 13.83, 13.81. For compound **2g**: HRMS (ESI) *m*/*z* calcd for $C_{42}H_{65}O_6$ (M^++1) 665.4781, found 665.4784; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 1.5 Hz, 1H), 7.26 (dd, *J* = 2.0, 8.5 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 6.79 (d, *J* = 8.5 Hz, 1H), 6.07 (q, *J* = 7.0 Hz, 1H), 4.06-4.01 (m, 4H), 3.90 (s, 6H), 3.61-3.55 (m, 1H), 3.44 (dd, *J* = 7.5, 17.0 Hz, 1H), 3.22 (dd, *J* = 7.0, 17.0 Hz, 1H), 1.92 (d, *J* = 7.0 Hz, 3H), 1.87-1.81 (m, 4H), 1.46-1.42 (m, 4H), 1.39-1.21 (m, 27H), 0.88 (t, *J* = 7.0 Hz, 6H). For compound **2h**: HRMS (ESI) *m*/*z* calcd for $C_{28}H_{33}O_6$ (M^++1) 465.2277, found 465.2278; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.52 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 1.5 Hz, 1H), 7.28 (dd, *J* = 1.5, 8.5 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.81 (d, *J* = 8.5 Hz, 1H), 6.12-6.03 (m, 2H), 6.05 (q, *J* = 7.0 Hz, 1H), 5.45-5.39 (m, 2H), 5.31-

5.28 (m, 2H), 4.64-4.61 (m, 4H), 3.90 (s, 6H), 3.58-3.53 (m, 1H), 3.43 (dd, J = 7.0, 16.5 Hz, 1H), 3.19 (dd, J = 7.0, 16.5 Hz, 1H), 1.91 (d, J = 7.0 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.59, 198.28, 153.47, 152.83, 147.71, 147.42, 144.04, 136.79, 132.83, 132.75, 131.65, 130.35, 124.73, 123.08, 118.41, 118.40, 113.81, 112.01, 110.19, 109.88, 69.67, 69.66, 55.97 (2x), 42.88, 29.71, 19.54, 13.79. For compound **2i**: HRMS (ESI) *m*/*z* calcd for $C_{36}H_{37}O_6$ (M^++1) 565.2590, found 565.2593; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, J = 2.0, 8.5 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.47-7.43 (m, 4H), 7.38-7.28 (m, 8H), 6.85 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 5.95 (q, J = 7.0 Hz, 1H), 5.20-5.11 (m, 4H), 3.92 (s, 3H), 3.91 (s, 3H), 3.56-3.49 (m, 1H), 3.38 (dd, J = 7.5, 16.5 Hz, 1H), 3.16 (dd, J = 6.5, 16.5 Hz, 1H), 1.84 (d, J = 7.0 Hz, 3H), 1.27 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.58, 198.21, 153.71, 153.06, 147.90, 147.46, 143.93, 136.72, 136.63, 136.56, 131.62, 130.34, 128.54 (2x), 128.52 (2x), 127.95, 127.92, 127.53 (2x), 127.38 (2x), 124.76, 123.23, 114.58, 112.58, 110.35, 110.15, 70.80, 70.76, 56.00 (2x), 42.86, 29.75, 19.53, 13.75. For compound **2j**: HRMS (ESI) *m*/*z* calcd for $C_{26}H_{33}O_8$ (M^++1) 473.2176, found 473.2180; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (s, 2H), 6.89 (s, 2H), 6.16 (q, J = 7.0 Hz, 1H), 3.89 (s, 6H), 3.88 (s, 6H), 3.87 (s, 3H), 3.84 (s, 3H), 3.60-3.53 (m, 2H), 3.18-3.12 (m, 1H), 1.95 (d, J = 7.0 Hz, 3H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.89, 198.58, 152.94 (2x), 152.59 (2x), 143.95, 142.45, 141.51, 138.55, 134.32, 132.42, 107.16 (2x), 105.56 (2x), 60.86 (2x), 56.20 (2x), 56.16 (2x), 42.90, 29.80, 19.67, 13.98. For compound **2k**: HRMS (ESI) *m*/*z* calcd for $C_{22}H_{23}F_2O_4$ (M^++1) 389.1565, found 389.1566; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (ddd, J = 1.0, 2.0, 8.5 Hz, 1H), 7.70 (dd, J = 2.0, 12.0 Hz, 1H), 7.46 (d, J = 10.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.10 (q, J = 7.0 Hz, 1H), 3.93 (s, 6H), 3.58-3.52 (m, 1H), 3.44 (dd, J = 7.5, 17.0 Hz, 1H), 3.19 (dd, J = 6.5, 17.0 Hz, 1H), 1.94 (d, J = 7.0 Hz, 3H), 1.29 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.66, 197.12, 152.95, 151.79, 151.08, 150.59, 143.81, 137.87, 131.96, 130.58, 127.08, 125.54, 117.42, 115.72, 112.16, 111.96, 56.25, 56.24, 42.89, 29.50, 19.48, 13.92.

6. (a) Henry, G. D. *Tetrahedron* **2004**, *60*, 6043. (b) Jones, G. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Ed.; Pergamon: New York, 1984; Vol. 2, p 395. (c) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Tymoshenko, D. O.; Essawy, S. A. *Synthesis* **1999**, 2114. (d) Chiu, C. F.; Tang, Z. L.; Ellingboe, J. W. *J. Comb. Chem.* **1999**, *1*, 1.
7. (a) Eun, J. K.; Ko, S. Y. *Bioorg. Med. Chem.* **2005**, *13*, 4103. (b) Patra, A.; Batra, S.; Kundu, B.; Joshi, B. S.; Roy, R.; Bhaduri, A. P. *Synthesis* **2001**, 276. (c) Pontikis, R.; Dolle, V.; Guillaumel, J.; Dechaux, E.; Note, R.; Nguyen, C. H.; Legraverend, M.; Bisagni, E.; Aubertain, A.-M.; Grierson, D. S.; Monneret, C. *J. Med. Chem.* **2000**, *43*, 1927. (d) Kobayashi, J.; Sekiguchi, M.; Shigemori, H.; Ohsaki, A. *J. Nat. Prod.* **2000**, *63*, 375.