Chinese Chemical Letters Vol. 12, No. 11, pp 955 – 956, 2001
http://www.imm.ac.cn/journal/ccl.html

A Convenient and Stereospecific Synthesis of (*Z*)-Benzylidenephthalides

Zhi Wei WANG, Shao Bai LI*

National Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000

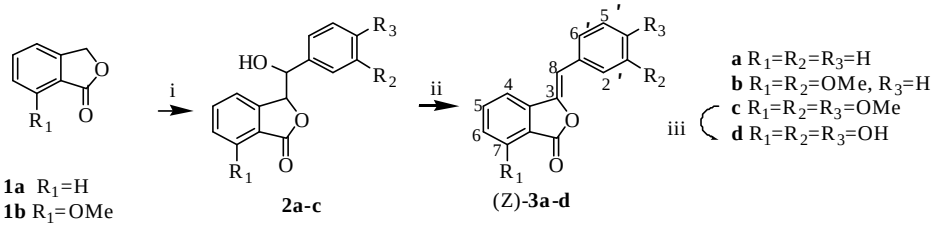
Abstract: A convencient and stereospecific synthesis of (*Z*)-benzylidenephthalides, including thunberginol F, from phthalides is described.

Keywords: Benzylidenephthalides , phthalides, synthesis.

Several 3-benzylidenephthalides have been isolated from natural sources[1-2]. Some of them are known to possess useful biological activity[1] and are also valuable intermediates[3] for the synthesis of naturally occurring biologically active compound.

Most of the natural 3-benzylidenephthalides exist in the (*Z*)-configuration. Synthe-tic methods for construction of a 3-benzylidene-phthalide skeleton have been developed[4]. Some of these methods for synthesizing highly oxygen-functionalized compounds seem to be impractical or fail to give satisfactory yield and other methods lead to a mixture of (*E*)- and (*Z*)- isomers. Herein, we report a novel, general method for synthesis of (*Z*)-3-benzylidene-phthalides.

Scheme 1



1a R_1=H
1b R_1=OMe

i) LDA,THF then aromatic aldehydes,-78℃;
ii) *p*-TsOH,C_6H_6,reflux; iii) BBr_3,CH_2Cl_2,-78℃-10℃

2a-c was obtained from **1a-c** in 71-86% yield. Dehydration of **2a-c** with *p*-TsOH provided 3-benzylidenephthalides **3a-c** in 80- 95% yield. The double bond of **3a-c** were shown to be (*Z*)-configuration. This was indicated by δ_H of the vinyl protons of **3a-c** (δ 6.40, 6.37 and 6.35 ppm, respectively). M. Watanabe *et al.*[5] reported that the chemical shifts of the vinyl protons of unstable (*E*)-isomers of 3-benzylidenephtha-

* E-mail: bsli@lzu.edu.cn

lides are shifted downfield from the corresponding stable (*Z*)-isomers. The vinyl protons of (*E*)-isomers and (*Z*)-isomers of 3-benzylidenephthalides appear at about 6.80 ppm and 6.35 ppm respectively. In addition, demethylation of compound **3c** with BBr_3 led to form thunberginol F (**3d**), which was isolated from *Hydrangea Dulcis Folium* and has (*Z*)-configuation[1]. This result confirmed that 3**a-c** were in the (*Z*)-configuation[6].

References and notes

1. M. Yoshikawa, E. Uchida, N. Chatani, N. Murakami, J. Yamahara, *Chem. Pharm. Bull.*, **1992**, *40*, 3121.
2. T. Sakamoto, M. Annaka, Y. Kondo , H. Yamanaka, *Chem. Pharm. Bull.*, **1986**, *34*, 2754.
3. M. Watanabe, H. Morimoto, U. Iwanaga, *Synthesis*, **1994**, 1083, and references cited therein.
4. a) C. E. Castro, E. J. Gaughan, D. C. Owsely, *J. Org. Chem.*, **1966**, *31*, 4071. b) O.Villemin, D. Goussu, *Heterocycles*, **1989**, *29*, 1255. c) S. Ohta, Y. Kamata, T. Inagaki, Y. Masuda, S. Yamamoto, M. Yamashita, I. Kawasaki, *Chem. Pharm. Bull.*, **1993**, *41*, 1188.
5. M. Watanabe, S. Ijichi, H. Morimoto, K. Nogami, ~S Furukawa, *Heterocycles*, **1993**, *36*, 553.
6. **2a** (78%): white solid, mp 144-146°C. IR (KBr, cm^{-1}): 3435, 1745, 1613, 1396, 1061. ^{1}HNMR (acetone-d6, δ ppm): 2.88 (br, s, 1H, OH, D_2O exchangeable), 5.20 (d,1H, *J*=4.8 Hz, H-8), 5.75 (d, 1H, *J*=4.8 Hz, H-3), 7.0-8.0 (m, 9H, HAr). MS (FAB) *m/z*: 241 (M+1, 95), 223 (M-17, 100). (Found: C, 74.74%; H, 5.25%. $C_{15}H_{12}O_3$ requires C, 74.99%; H, 5.03%). **2b** (86%): white solid, mp 140-142°C. IR (KBr, cm^{-1}): 3426, 1764, 1610, 1514, 1491, 1248. ^{1}HNMR ($CDCl_3$, δ ppm): 2.40 (br, s, 1H, OH, D_2O exchangeable), 3.80, 3.94 (s, 6H, 2×OCH_3), 5.13 (d, 1H, *J*=4.8 Hz, H-8), 5.55 (d, 1H, *J*=4.8 Hz, H-3), 6.50 (d, 1H, *J*=8.0 Hz, H-6), 6.86 (d, 3H, *J*=8.0 Hz, H-3´, H-5´ and H-4), 7.25 (d, 2H, *J*=8.0 Hz, H-2´ and H-6´), 7.45 (t, 1H, *J*=8.0 Hz, H-5). MS (FAB) *m/z*: 301 (M+1, 57), 283 (100), 255 (65). (Found: C, 68.12%; H, 5.50%. $C_{17}H_{16}O_5$ requires C, 67.99%; H,5.37%). **2c** (71%): white solid, mp 172-176°C. IR (KBr, cm^{-1}): 3387, 1759, 1598, 1515, 1488, 1465, 1420, 1273, 1138, 1072, 1051, 1024, 1001. ^{1}HNMR ($CDCl_3$, δ ppm): 2.95 (br, s, 1H, OH, D_2O exchangeable), 3.82, 3.87 (s, 9H, 3×OCH_3), 5.16 (d, 1H, *J* = 4.8 Hz, H-8), 5.57 (d, 1H, *J*=4.8 Hz, H-3), 6.43 (d, 1H, *J*=8.0 Hz, H-5´), 6.50-6.70 (m, 4H, H-2´, H-4´, H-6 and H–6´), 7.43 (t, 1H, *J*=8.0 Hz, H-5). MS (FAB) *m/z*: 331 (M+1, 87), 313 (100), 285 (50). (Found: C, 65.57%; H, 5.44%. $C_{18}H_{18}O_6$ requires C, 65.45%; H, 5.49%.). **3a** (80%): white solid. mp 88-89°C. (lit[2]: 95-97°C). IR(KBr, cm^{-1}): 1779, 1655, 1603, 971. ^{1}HNMR ($CDCl_3$, δ ppm): 6.40 (s, 1H, H-8), 7.3-8.0 (m, 9H, HAr). MS(FAB)*m/z*: 223 (60), 222 (M^+, 55). (Found: C, 80.82%; H, 4.66%. $C_{15}H_{10}O_2$ requires C, 81.07%; H, 4.54%). **3b** (85%): white solid. mp 187-188°C. IR(KBr, cm^{-1}): 1770, 1654, 1600, 1491, 1258. ^{1}HNMR ($CDCl_3$, δ ppm): 3.87 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 6.37 (s, 1H, H-8), 6.93 (d, 1H, *J*=7.5 Hz, H-6), 6.95 (d, 2H, *J*=8.9 Hz, H-3´ and H–5´), 7.30 (d, 1H, *J*=7.5 Hz, H-4), 7.66 (t, 1H, *J*=7.5 Hz, H-5), 7.83 (d, 2H, *J*=8.9 Hz, H-2´ and H-6´). MS(FAB)*m/z* : 283 (M+1, 85), 282 (M^+, 90). (Found: C, 72.51%; H, 5.20; $C_{17}H_{14}O_4$ requires C, 72.33%; H, 5.00%). **3c** (95%): yellowish solid. mp 186-188°C (lit[1]: amorphous powder). IR(KBr, cm^{-1}): 2920, 1771, 1600, 1515, 1259. ^{1}HNMR ($CDCl_3$, δ ppm): 3.93, 3.98, 4.03 (3s, 9H, 3×OCH_3), 6.35 (s, 1H, H-8), 6.90 (d, 1H, *J*=8 Hz, H-5´), 6.92 (br, s, 1H, *J*=8 Hz, H-6), 7.29 (br, s, 1H, *J*=8 Hz, H-4), 7.40 (br, d, 1H, *J*=8 Hz, H-6´), 7.46 (br, s, 1H, H-2´), 7.64 (t, 1H, *J*=8 Hz, H-5). MS(FAB)*m/z*: 312 (M^+, 100), 297 (35), HRMS: Cacld. for $C_{18}H_{16}O_5$: 312.0998, Found: 312.0986. **3d** (86%) yellowish solid. mp 240-243°C (lit[1]: 242-243°C). IR (KBr, cm^{-1}): 3274, 1737 (C=O), 1604. ^{1}HNMR (DMSO-d6, δ ppm): 6.62 (s, 1H, H-8), 6.80 (d, 1H, *J* = 8 Hz, H-5´), 6.91 (br, d, 1H, *J*=8 Hz, H-6), 7.05 (br, d, 1H, *J*=8 Hz, H-6´), 7.39 (br, s, 1H, H-2´), 7.41 (br, d, 1H, *J*=8 Hz, H-4), 7.58 (t, 1H, *J*=8 Hz, H-5). MS(FAB) *m/z* : 270 (M^+, 100). (Found: C, 66.46%; H, 4.01%. $C_{15}H_{10}O_5$ requires C, 66.67%; H, 3.73%).

Received 27 March, 2001