

Synthesis of Naturally Occurring (*Z*)-3-Benzylidenephthalide and (\pm) 3-Benzylphthalides†

Raghao S. Mali,* Archna P. Massey and Manohar I. Talele

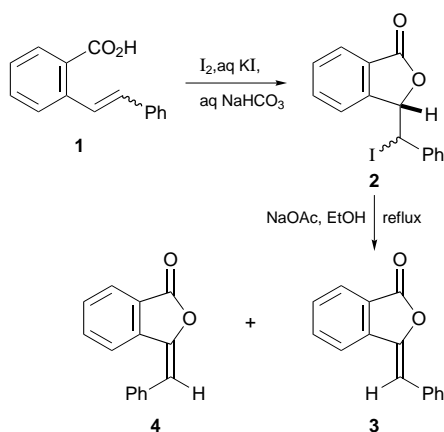
Garware Research Centre, Department of Chemistry, University of Pune, Pune 411 007, India

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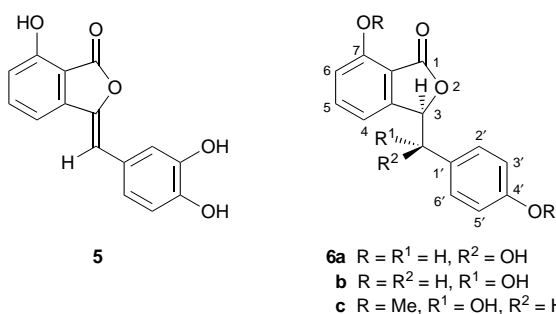
A convenient method, involving the generation of the phthalide anion, is described for the synthesis of naturally occurring (*Z*)-3-benzylidenephthalide (**5**) and (\pm) 3-benzylphthalides (**6c**, **10a–c**), starting from phthalides (**7a** and **7b**).

3-Benzylidenephthalides are found to be synthetically useful intermediates for a wide variety of carbocyclic and heterocyclic compounds including some alkaloids.¹ The (*Z*)-3-benzylidenephthalide (thunberginol-F **5**),² 3-benzylphthalides^{3–5} (balantiolide **10a**) and related phthalides (**10b**, **10c** and **10e**) and hydramacrophyllols A and B (**6a** and **6b**) have been isolated from natural sources. These phthalides are valuable as they possess interesting biological activities. In view of the importance of 3-benzylidenephthalides, several general methods are reported for their synthesis.⁸ Since the isolation² of thunberginol-F **5** in 1992, three methods have been reported for its synthesis.^{11–13} However, the naturally occurring 3-benzylphthalides **10a–c** have not been synthesised so far.

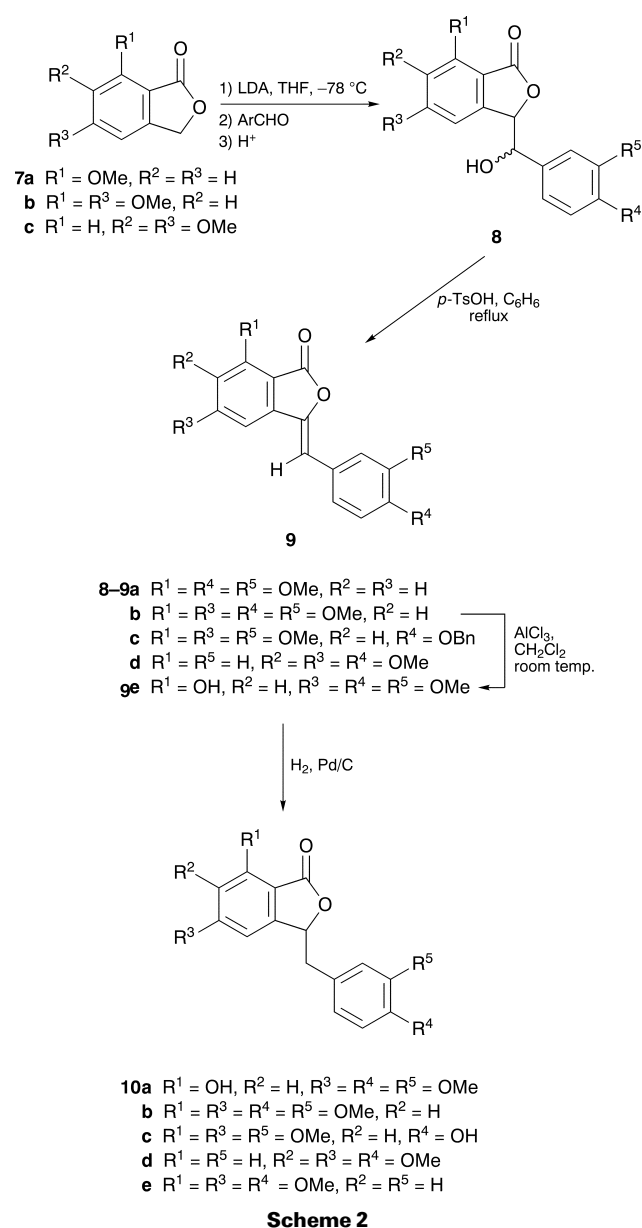
Since considerable work has been done in our laboratory on the synthesis of naturally occurring 3-alkylidenephthalides using the iodolactonisation approach, the approach was extended to the synthesis of 3-benzylidenephthalides¹⁵ (Scheme 1). The 3-benzylidenephthalides (**3** and **4**) were obtained in 13 and 12% yields respectively. The stereochemistry of the 3-benzylidenephthalides (**3** and **4**) was determined by ¹H NMR. As the yields by this approach were



Scheme 1



poor, the syntheses of thunberginol-F **5** (\pm) 3-benzylphthalides **10a–c** and the dimethyl ether **6c** of hydramacrophyllols **6a** and **6b** have been achieved using the phthalide anion route (Scheme 2).



Scheme 2

For the synthesis of thunberginol-F, the anion of phthalide **7a**,¹⁹ generated *in situ*¹⁸ using LDA in THF at -78 °C was treated with veratraldehyde. The hydroxyphthalide **8a** was obtained as a mixture of diastereoisomers (1:1.6), in 55% yield. Dehydration of **8a** using toluene-*p*-sulfonic acid in refluxing benzene gave the trimethyl ether of thunberginol-F, **9a**, mp 186 °C (lit.,¹³ 186–188 °C). The conversion of

*To receive any correspondence (e-mail: rsmali@chem.unipune.ernet.in).

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9a to thunberginol-F **5** using BBr_3 has already been reported in the literature.^{12,13}

The syntheses of balantiolide **10a** and related phthalides **10b** and **10c** have been achieved from phthalide **7b**. The anion of 5,7-dimethoxyphthalide (**7b**) was reacted with veratraldehyde and 4-benzyloxy-3-methoxybenzaldehyde to obtain the hydroxyphthalides **8b** and **8c**. These phthalides **8b** and **8c** on dehydration using toluene-*p*-sulfonic acid gave the (*Z*)-3-benzylidenephthalides **9b** and **9c** which were hydrogenated, to give (\pm) *O*-methylbalantiolide (**10b**) and the (\pm) 3-benzylphthalide (**10c**) in 84 and 77% yields respectively.

The naturally occurring 3-benzylphthalide, balantiolide (**10a**), has been synthesised from the benzylidenephthalide **9b** via the intermediacy of **9e**. The tetramethoxy 3-benzylidenephthalide **9b** was reacted with AlCl_3 in methylene chloride at room temperature, to give phthalide **9e** in 82% yield. Hydrogenation of **9e** using 10% Pd/C in ethyl acetate gave the (\pm) 3-benzylphthalide **10a** in 71% yield.

The 5,6-dimethoxyphthalide (**7c**)²¹ on similar sequence of reactions provided (\pm) 3-(4-methoxybenzyl)-5,6-dimethoxyphthalide (**10d**), via the 3-hydroxyphthalide **8d** and 3-benzylidenephthalide **9d**.

Using the phthalide anion approach the synthesis of **6c**, a dimethyl ether of **6a** and **6b**, has been achieved in 73% yield from phthalide **7a**.

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Techniques used: IR, ^1H NMR, elemental analysis, TLC and column chromatography

References: 22

Schemes: 2

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References cited in this synopsis

- (a) R. A. Aitken, H. R. Cooper and A. P. Mehrotra, *J. Chem. Soc., Perkin Trans. 1* 1996, 475; (b) Y. Masahisa, K. Kenshi, K. Takaki, A. Michitaka, K. Toshio and O. Nobuhiro, *J. Med. Chem.*, 1993, **36**, 4052; (c) T. Nishio, *J. Chem. Soc., Perkin Trans. 1*, 1995, 561; (d) E. Napolitano, R. Fiaschi, V. Scartoni and A. Marsili, *J. Chem. Soc., Perkin, Trans. 1*, 1986, 781.
- M. Yoshikawa, E. Uchida, N. Chatani, N. Murakami and J. Yamahara, *Chem. Pharm. Bull.*, 1992, **40**, 3121.
- L. Kraut, R. Mues and M. Sim Sim, *Phytochemistry*, 1994, **37**, 1337.
- Y. Asakawa, K. Takikawa, M. Tori and E. O. Campbell, *Phytochemistry*, 1986, **25**, 2543.
- (a) Y. Asakawa, K. Takikawa and M. Tori, *Phytochemistry* 1987, **26**, 1023; (b) personal communication from Professor Asakawa.
- (a) M. Noda, M. Yamaguchi, E. Ando, K. Takeda and K. Nokihara, *J. Org. Chem.*, 1994, **59**, 7968; (b) B. S. Joshi, Q. Jiang, T. Rho and S. W. Pelletier, *J. Org. Chem.*, 1994, **59**, 8220; (c) T. A. Crabb and A. Patel, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2783; (d) N. E. Cundasawmy and D. B. MacLean, *Can. J. Chem.*, 1972, **50**, 3028; (e) T. Takada and S. Ohki, *Chem. Pharm. Bull.*, 1971, **19**, 977.
- S. Ohta, Y. Kamata, T. Inagaki, Y. Masuda, S. Yamamoto, M. Yamashita and I. Kawasaki, *Chem. Pharm. Bull.*, 1993, **41**, 1188.
- M. Yoshikawa, E. Harada, N. Yagi, Y. Okuno, O. Muraoka, H. Aoyama and N. Murakami, *Chem. Pharm. Bull.*, 1994, **42**, 721.
- Zhi-Wei Wang, Shao-Bai Li and Yu-Lin Li, *Indian J. Chem.*, 1996, **35B**, 363.
- M. I. Talele, M. Phil. Dissertation, University of Pune, 1986.
- R. S. Mali, P. G. Jagtap, S. R. Patil and P. N. Pawar, *J. Chem. Soc. Chem. Commun*, 1992, 883.
- R. S. Mali, P. G. Jagtap and S. G. Tilve, *Synth. Commun*, 1990, **20**, 2641.
- J. A. McRae, R. B. VanOrder, F. H. Griffiths and T. E. Habgood, *Can. J. Chem.*, 1951, **29**, 482.