Pergamon

Tetrahedron Letters 42 (2001) 1147–1149

TETRAHEDRON
LETTERS

# A novel Baylis–Hillman protocol for the synthesis of functionalized fused furans

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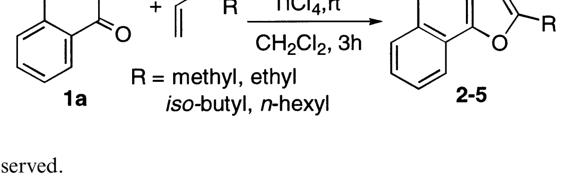
Received 13 November 2000; accepted 27 November 2000

**Abstract**—Titanium tetrachloride mediated Baylis–Hillman reaction of aryl 1,2-diones with α,β-unsaturated ketones leads to the formation of an interesting class of functionalized fused furans. © 2001 Elsevier Science Ltd. All rights reserved.

The Baylis–Hillman reaction is an emerging three-component reaction involving the construction of a carbon–carbon bond between the α-position of activated alkenes and carbon electrophiles under the catalytic influence of tertiary amines, particularly DABCO, to provide an interesting class of densely functionalized molecules, which have been successfully employed in the development of various stereoselective transformation methodologies.[1–11] Fused furan derivatives constitute an important class of molecule because of the presence of this structural framework in various biologically active and natural products.[12–19] Hence, the development of a simple and convenient methodology for the synthesis of these interesting fused furans has been, and continues to be, an important synthetic endeavor in organic chemistry.[17–22] In a continuation of our ongoing research program in the development of new synthetic transformations using Baylis–Hillman chemistry,[8–11] we herein report a convenient and simple methodology for the synthesis of functionalized fused furans via the reaction between aryl 1,2-diones and alkyl vinyl ketones under the influence of titanium tetrachloride.

Though various electrophiles have been extensively used in the Baylis–Hillman coupling reaction, application of aryl 1,2-diketones as electrophiles has not been systematically explored so far.[23] Our attempts to use phenanthrene-9,10-dione (aryl 1,2-dione) as an electrophile in the DABCO catalyzed Baylis–Hillman coupling with activated alkenes, such as acrylonitrile and methyl vinyl ketone, were unsuccessful. There has been an increasing interest in recent years in the development of new catalytic reagent systems, other than tertiary amines, to perform the Baylis–Hillman construction of carbon–carbon bonds.[24–26] Recently, titanium tetrachloride mediated Baylis–Hillman couplings of alkyl vinyl ketones with aldehydes and α-keto esters have been described.[27–29] It occurred to us that titanium tetrachloride might mediate coupling between aryl 1,2-diones and activated alkenes. Accordingly, we first carried out the reaction of phenanthrene-9,10-dione **1a** with methyl vinyl ketone (mvk) under various conditions. The best results were obtained when phenanthrene-9,10-dione **1a** (1 mM) was treated with mvk (3 mM) in the presence of titanium tetrachloride (1 mM) in dichloromethane at room temperature for 3 h, which provided 2-methylphenanthro[9,10-*b*]furan-3-carboxaldehyde **2** in 70% yield.[30] The structure of this compound was also confirmed by single-crystal X-ray data[31] (Fig. 1). The formation of the fused furan **2** is a pleasant surprise to us in the sense that this is not the usual Baylis–Hillman adduct. Encouraged by this result, we have carried out the reaction of representative alk-1-en-3-ones with phenanthrene-9,10-dione **1a** under similar conditions thus providing a simple synthesis of 2-alkylphenanthro[9,10-*b*]furan-3-carboxaldehydes **3**–**5** (Table 1 and Eq. (1)).



(1)

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*Keywords*: Baylis–Hillman reaction; fused furans; α,β-unsaturated ketones; titanium tetrachloride.

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PII: S0040-4039(00)02175-4

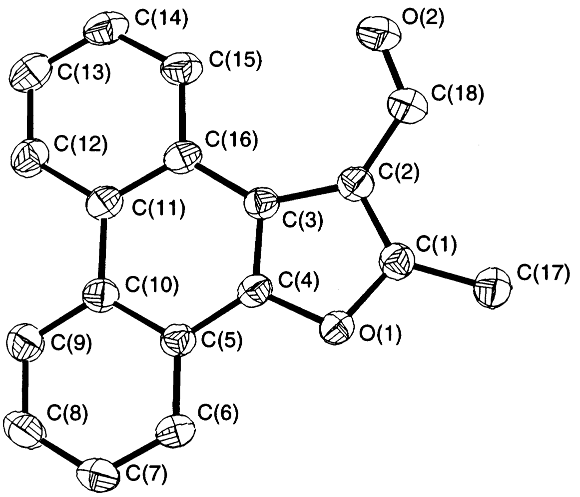


**Figure 1.** ORTEP diagram of compound **2**.

**Table 1.** Syntheses of 2-alkylphenanthro[9,10-*b*]furan-3-carboxaldehydes and 2-alkylpyreno[4,5-*b*]furan-3-carboxaldehydes[a,b]

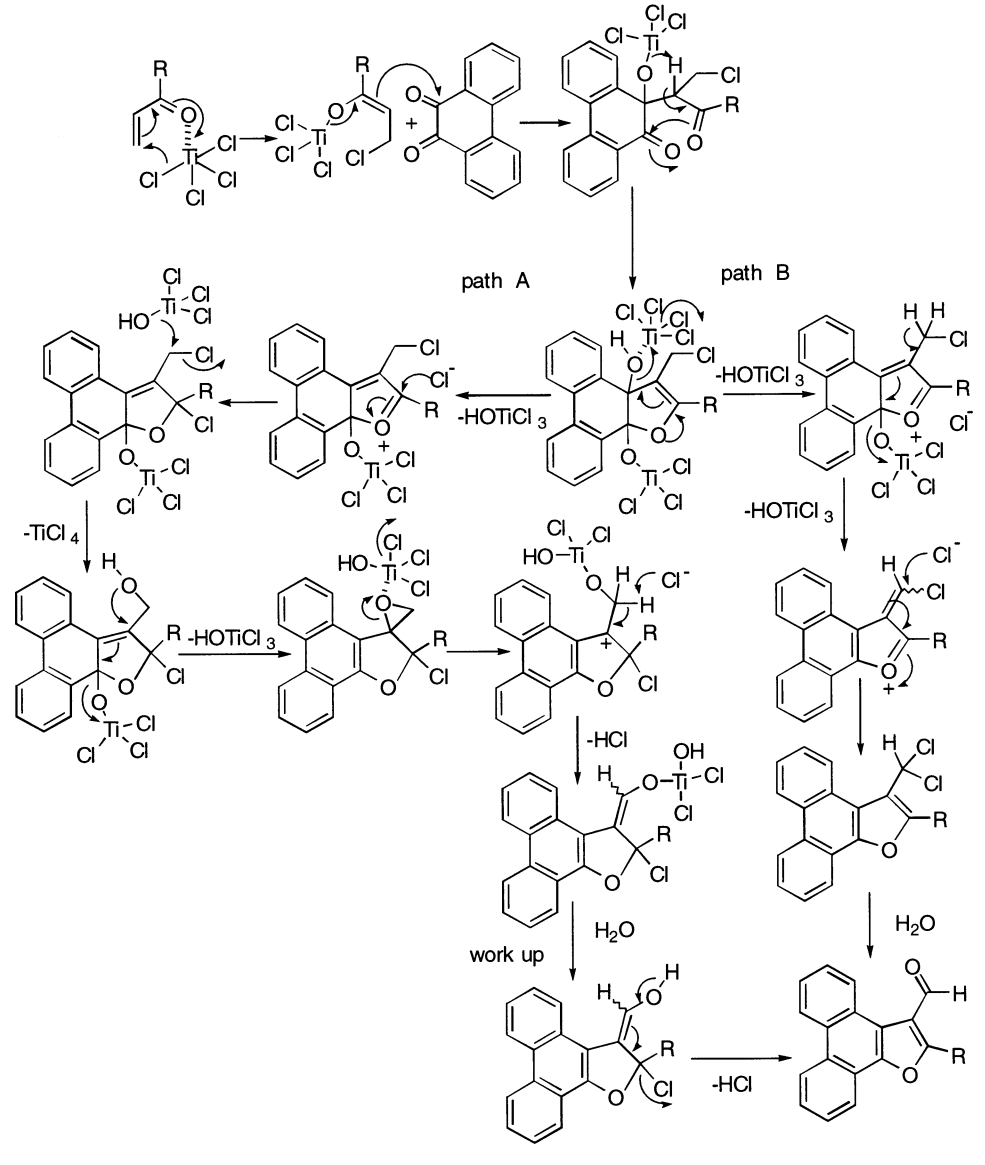
| 1, 2-Dione | Enone | Product | Mp (°C) | Yield[c] (%) |
|---|---|---|---|---|
| **1a** | Methyl vinyl ketone | **2**[d] | 183 | 70 |
| **1a** | Ethyl vinyl ketone | **3** | 136–138 | 62 |
| **1a** | *i*-Butyl vinyl ketone | **4** | 142–144 | 54 |
| **1a** | *n*-Hexyl vinyl ketone | **5** | 80–82 | 45 |
| **1b** | Methyl vinyl ketone | **6** | 154–156 | 43 |
| **1b** | Ethyl vinyl ketone | **7** | 98–100 | 25 |
| **1b** | *i*-Butyl vinyl ketone | **8** | 136–137 | 16 |

[a] All reactions were carried out on a 1 mmol scale (aryl 1,2-diones) with enone (3 mmol) and $TiCl_4$ (1 mmol) at room temperature for 3 h.

[b] All products (**2**–**8**) were obtained as solids and were characterized by IR, $^1H$ NMR (200 MHz), $^{13}C$ NMR (50 MHz), mass spectroscopy and elemental analyses.

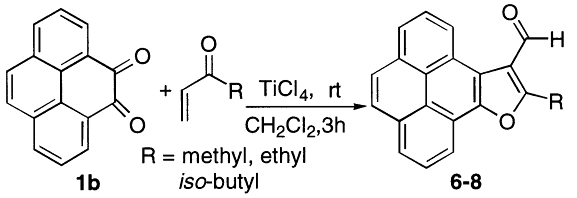
[c] Yields of products (based on aryl 1,2-diones) after purification by column chromatography (silica gel, 4% EtOAc in hexanes).

[d] The structure of compound **2** was also confirmed by single-crystal X-ray data.



**Scheme 1.**

With a view to understanding the generality of the reaction we have also examined the utility of pyrene-4,5-dione **1b** as an electrophile for coupling with alkyl vinyl ketones, thus providing a simple procedure for the preparation of the desired 2-alkylpyreno[4,5-*b*]furan-3-carboxaldehydes **6–8** (Table 1 and Eq. (2)) in reasonable yields. A possible mechanism (path A and B) for the formation of the products is shown in Scheme 1.



(2)

In conclusion, this methodology, for the first time, describes the Baylis–Hillman reaction between aryl 1,2-diones and alk-1-en-3-ones in the presence of titanium tetrachloride, thus providing a new protocol for the synthesis of functionalized fused furans.

## Acknowledgements

We thank DST (New Delhi) for funding this project. We thank UGC (New Delhi) for a Special Assistance Program in Organic Chemistry in the School of Chemistry, University of Hyderabad. B.S. thanks CSIR (New Delhi) and J.S.R. thanks UGC (New Delhi) for financial support. We also thank the National Single Crystal X-Ray Facility, School of Chemistry, University of Hyderabad, funded by DST (New Delhi).

## References

1. Basavaiah, D.; Dharma Rao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001–8062.
2. Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670.
3. Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp. 201–350.
4. Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCauge, R. *J. Org. Chem.* **1998**, *63*, 7183–7189.
5. Chamakh, A.; Amri, H. *Tetrahedron Lett.* **1998**, *39*, 375–378.
6. Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613–2616.
7. Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220.
8. Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Sarma, P. K. S.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197–1200.
9. Basavaiah, D.; Bakthadoss, M.; Pandiaraju, S. *Chem. Commun.* **1998**, 1639–1640.
10. Basavaiah, D.; Krishnamacharyulu, M.; Suguna Hyma, R.; Pandiaraju, S. *Tetrahedron Lett.* **1997**, *38*, 2141–2144.
11. Basavaiah, D.; Kumaragurubaran, N.; Padmaja, K. *Synlett* **1999**, 1630–1632.
12. Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44–122.
13. Tasker, A. S.; Sorensen, B. K.; Jae, H. S.; Winn, M.; von Geldern, T. W.; Dixon, D. B.; Chiou, W. J.; Dayton, B. D.; Calzadila, S.; Hernandez, L.; Marsh, K. C.; WuWong, J. R.; Opgenorth, T. J. *J. Med. Chem.* **1997**, *40*, 322–330.
14. Gammill, R. B.; Bell, F. P.; Bell, L. T.; Bisaha, S. N.; Wilson, G. J. *J. Med. Chem.* **1990**, *33*, 2685–2687.
15. Achenbach, H.; Groß, J.; Dominguez, X. A.; Cano, G.; Star, J. V.; Del, L.; Brussolo, C.; Munoz, G.; Salgado, F.; Lopez, L. *Phytochemistry* **1987**, *26*, 1159–1166.
16. Dow, R. L.; Bechle, B. M.; Chou, T. T.; Clark, D. A.; Hulin, B.; Stevenson, R. W. *J. Med. Chem.* **1991**, *34*, 1538–1544.
17. Hirota, H.; Kitano, M.; Komatsubara, K.; Takahashi, T. *Chem. Lett.* **1987**, 2079–2080.
18. Inoue, M.; Frontier, A. J.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 761–764.
19. Yang, Z.; Hon, P. M.; Chui, K. Y.; Xu, Z. L.; Chang, H. M.; Lee, C. M.; Cui, Y. X.; Wong, H. N. C.; Poon, C. D.; Fung, B. M. *Tetrahedron Lett.* **1991**, *32*, 2061–2064.
20. Gammill, R. B.; Hyde, B. R. *J. Org. Chem.* **1983**, *48*, 3863–3865.
21. Nicolaou, K. C.; Snyder, S. A.; Bigot, A.; Pfefferkorn, J. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 1093–1096.
22. Ledoussal, B.; Gorgues, A.; Coq, A. L. *Tetrahedron* **1987**, *43*, 5841–5852.
23. Non-enolizable aliphatic 1,2-diones were used as electrophiles in the Baylis–Hillman reaction. See: Strunz, G. M.; Bethell, R.; Sampson, G.; White, P. *Can. J. Chem.* **1995**, *73*, 1666–1674.
24. Kataoka, T.; Iwama, T.; Tsujiyama, S. *Chem. Commun.* **1998**, 197–198.
25. Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synlett* **1999**, 1249–1250.
26. Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun.* **1998**, 1271–1272.
27. Li, G.; Wei, H. X.; Gao, J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1–5.
28. Li, G.; Gao, J.; Wei, H. X.; Enright, M. *Organic Lett.* **2000**, *2*, 617–620.
29. Basavaiah, D.; Sreenivasulu, B.; Mallikarjuna Reddy, R.; Muthukumaran, K. *Synth. Commun.*, accepted for publication.
30. Spectral data for compound **2**: IR (KBr): 1684 cm$^{-1}$; $^{1}$H NMR (200 MHz) (CDCl$_3$): $\delta$ 2.91 (s, 3H), 7.57–7.86 (m, 4H), 8.25–8.38 (m, 1H), 8.63–8.82 (m, 2H), 9.32–9.43 (m, 1H), 10.40 (s, 1H); $^{13}$C NMR (50 MHz): $\delta$ 13.45, 117.22, 120.46, 120.70, 121.10, 123.08, 123.19, 125.81, 126.53, 126.99, 127.17, 128.09, 128.57, 129.49, 148.50, 166.70, 184.65; $m/z$: 260 (m$^{+}$); analysis calculated for $C_{18}H_{12}O_2$: C, 83.06; H, 4.65; found: C, 83.12; H, 4.63. It appears that in the $^{13}$C NMR spectrum two carbons have the same chemical shift and hence we have observed 17 carbon signals only.
31. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (for compound **2** CCDC #144476). Crystal data for **2**: empirical formula, $C_{18}H_{12}O_2$; formula weight, 260.28; crystal color, habit: colorless, prism; crystal dimensions, 0.70×0.30×0.20 mm; crystal system, orthorhombic; lattice type, primitive; lattice parameters, $a=6.7814$ (19), $b=10.525$ (4), $c=17.668$ (10) Å; $V=1261.0$ (9) Å$^3$; space group, $P2_12_12_1$ (no. 19); $Z=4$; $D_{\text{calcd}}=1.371$ g/cm$^3$; $F_{000}=544.00$; (Mo K) = 0.71073 Å; residuals: $R=0.0451$, $R_w=0.1133$.