Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 1125–1128
Tetrahedron Letters

A facile synthesis of chromeno[4,3-*b*]pyrroles derived from allyl derivatives of Baylis–Hillman adducts through intramolecular 1,3-dipolar cycloaddition using ultrasonication

Ekambaram Ramesh, Raghavachary Raghunathan *

Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India

Received 18 October 2007; revised 4 December 2007; accepted 12 December 2007

Abstract

Synthesis of a series of chromene[4,3-*b*]pyrroles has been accomplished through an intramolecular 1,3-dipolar cycloaddition reaction of an azomethine ylide with the dipolarophile derived from Baylis–Hillman adducts. Improved yields of the same products were obtained when the reaction was carried out under ultrasonication.

Keywords: Baylis–Hillman adduct; Chromene pyrrole; Cycloaddition; Azomethine ylide

Intramolecular [3+2] cycloaddition of azomethine ylides has been used widely to construct complex cyclic systems from relatively simple precursors. This mode of cycloaddition simultaneously constructs two carbon–carbon bonds and forms complex ring systems with regio- and stereocontrol.[1–5]

α-Methylene-β-hydroxy esters **1a–f** are easily prepared by the Baylis–Hillman reaction[6,7] and are well-utilized as versatile building blocks for the stereoselective construction of natural products, including alkaloids,[8] macrolides,[9] terpenoids[10–12] and pheromones.[13–16]

Multifunctional allylic compounds such as **1a–f** and derivatives **2a–f** are useful scaffolds for the synthesis of a wide range of complex molecular frameworks.

With the objective of expanding the scope of these allyl halides in synthetic organic chemistry, we have used the allyl bromides derived from Baylis–Hillman adducts as dipolarophiles which had not been exploited previously as internal olefins for the intramolecular 1,3-dipolar cycloaddition reactions.

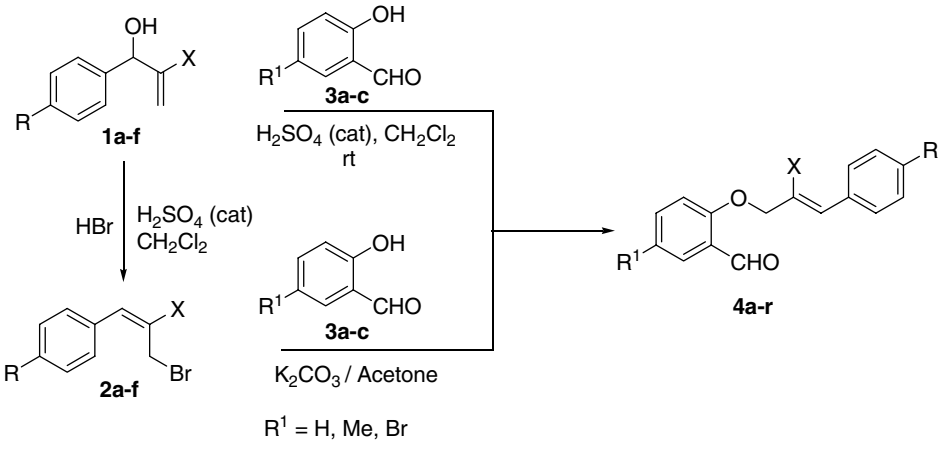
Activation of organic reactions with ultrasound constitutes an important domain of modern chemistry. This is largely due to the fact that sonochemistry and the recent upsurge of interest in sustainable chemistry share similar aims, such as the use of less hazardous chemicals and environmentally benign solvents, while minimizing energy consumption and increasing the selectivity of the product.[17,18] Although 1,3-dipolar cycloaddition reactions carried out under conventional methods have proved to be beneficial in terms of regio- and stereoselectivity, only a few reports are available on the use of ultrasonic irradiation in 1,3-dipolar cycloaddition.[19–21]

In continuation of our research in the area of 1,3-dipolar cycloaddition,[22–31] we herein report for the first time, the ultrasonic mediated synthesis of chromeno[4,3-*b*]pyrroles using allyl bromides derived from Baylis–Hillman adducts as dipolarophiles in an intramolecular cycloaddition reaction.

Treatment of Baylis–Hillman adducts **1a–f** with salicylaldehydes **3a–c** in the presence of a catalytic amount of H_2SO_4 in dichloromethane gave moderate yields of adducts **4a–r** (64–74%). However, synthesis of the same products **4a–r** could be accomplished in good yields by treating the allyl derivatives of Baylis–Hillman adducts **2a–f**[32] with

* Corresponding author. Tel.: +91 44 22208211; fax: +91 44 22300488.
E-mail address: ragharaghunathan@yahoo.com (R. Raghunathan).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.066



R = H, X=$COOCH_3$
R = Cl, X=$COOCH_3$
R = OMe, X=$COOCH_3$
R = H, X=CN
R = Cl, X=CN
R = OMe, X=CN

4a R = H, X=$COOCH_3$, R^1= H
4b R =Cl, X=$COOCH_3$, R^1= H
4c R = OMe, X =$COOCH_3$, R^1= H
4d R = H, X=$COOCH_3$, R^1= Br
4e R = Cl, X=$COOCH_3$, R^1= Br
4f R = OMe, X=$COOCH_3$, R^1= Br
4g R = H, X=$COOCH_3$, R^1= OMe
4h R = Cl, X=$COOCH_3$, R^1= OMe
4i R = OMe, X=$COOCH_3$, R^1= OMe

4j R = H, X=CN, R^1= H
4k R =Cl, X=CN, R^1= H
4l R = OMe, X=CN, R^1= H
4m R = H, X=CN, R^1= Br
4n R = Cl, X=CN, R^1= Br
4o R = OMe, X=CN, R^1= Br
4p R = OMe, X=CN, R^1= OMe
4q R = OMe, X=CN, R^1= OMe
4r R = OMe, X=CN, R^1= OMe

Scheme 1.

salicylaldehydes **3a**–**c** in the presence of K_2CO_3 and dry acetone (86–94%) in 3 h (Scheme 1).

The structural assignments of products **4a**–**r** were based on the analysis of NMR spectra. Thus compound **4b** exhibited a singlet at δ 3.79 for the methyl protons of the ester, a singlet at δ 4.88 for the OCH_2 protons, a singlet at δ 7.19 for the alkene hydrogen and a singlet at δ 10.35 for the aldehyde proton.[33] The *O*-allyl salicylaldehyde derivatives **4a**–**i** were refluxed with sarcosine in anhydrous methanol to give chromeno[4,3-*b*]pyrroles in moderate to good yields (70–78%)[34] (Scheme 2).

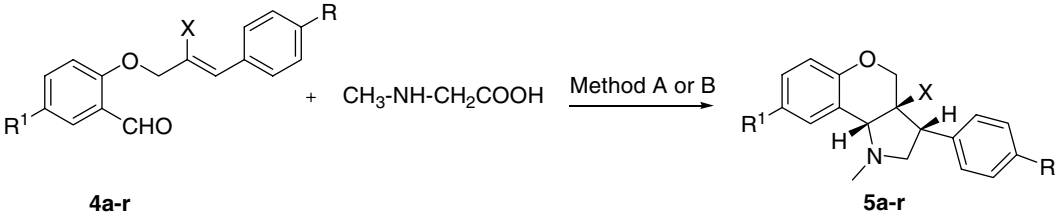
The structure and the regiochemistry of the cycloadducts were confirmed by spectral analysis. The IR spectrum of **5a** showed a sharp peak at 1744 cm^{-1} for the ester carbonyl. The ^1H NMR spectrum of **5a** showed doublets for each of the OCH_2 protons. The NCH_2 protons of the pyrrolidine protons appeared as doublet of doublets at δ 2.95 ($J = 9.9, 5.4$) and at δ 3.38 ($J = 9.9, 3.3$). The benzylic proton occurred as a doublet of doublets at δ 3.75 ($J = 3.3, 5.4$) and the ring junction proton appeared as a singlet at δ 3.67. Finally, the structure of **5a** was confirmed by mass spectrometry, which showed a peak at *m*/*z* 323.15. The assignment of *cis*-stereochemistry to the ring junction of all the cycloadducts was initially made by analogy with the stereochemistry observed in similar systems.[35,36]

Further, the X-ray structure of **5b** confirmed the *cis* stereochemistry at the ring junction (Fig. 1).[37]

To establish the generality of this cycloaddition reaction, we extended the method to salicylaldehyde derivatives **4j**–**r** containing a –CN moiety using similar conditions to give a series of cycloadducts **5j**–**r** in moderate to good yields. The structures and regiochemistry of the cycloadducts were similar to those of **5a**–**i** as confirmed by the spectroscopic data.

To improve the yield, we examined the reaction under two different conditions. Thus, the reactions of **4a**–**r** with sarcosine in methanol under reflux afforded cycloadducts **5a**–**r** in 68–78% yields, but required long reaction times and higher temperature.

When the same reactions were carried out under ultrasonic irradiation in methanol at room temperature, there was a dramatic increase in the yields of the products along



Scheme 2.

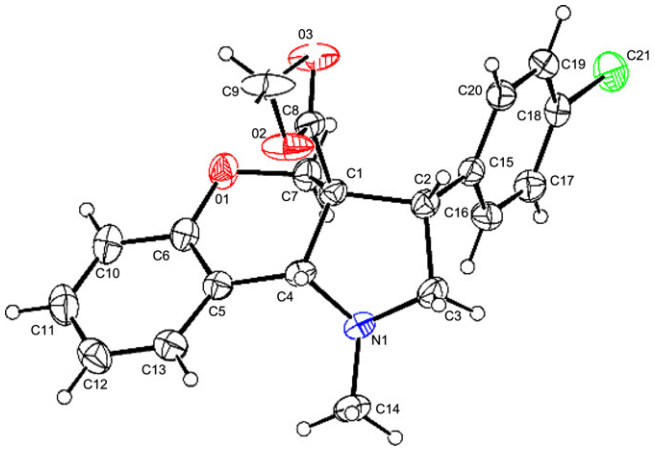


Fig. 1. ORTEP diagram of **5b**.

Table 1
Synthesis of chromeno[4,3-*b*]pyrrole derivatives using methods A and B

Entry	Chromeno [4,3-*b*] pyrroles			Method A		Method B	
	R	X	R^1	Time (h)	Yield (%)	Time (h)	Yield (%)
5a	H	$COOCH_3$	H	4.0	68	1.5	81
5b	Cl	$COOCH_3$	H	4.0	71	3.0	84
5c	OMe	$COOCH_3$	H	4.5	78	2.5	85
5d	H	$COOCH_3$	Br	5.0	65	3.0	81
5e	Cl	$COOCH_3$	Br	5.5	53	3.5	76
5f	OMe	$COOCH_3$	Br	6.5	51	4.5	71
5g	H	$COOCH_3$	OMe	7.0	65	4.0	77
5h	Cl	$COOCH_3$	OMe	7.5	77	5.0	82
5i	OMe	$COOCH_3$	OMe	8.0	73	5.5	85
5j	H	CN	H	3.0	71	1.0	85
5k	Cl	CN	H	4.0	69	3.0	82
5l	OMe	CN	H	4.5	71	2.5	89
5m	H	CN	Br	5.0	69	3.0	81
5n	Cl	CN	Br	5.5	64	3.5	77
5o	OMe	CN	Br	6.0	73	4.5	78
5p	OMe	CN	OMe	7.0	77	4.0	82
5q	OMe	CN	OMe	7.5	81	5.0	87
5r	OMe	CN	OMe	8.0	78	5.5	89

Method A: Methanol under reflux.
Method B: Methanol at rt under ultrasonic irradiation.

with a decrease in reaction time. Under these conditions, cycloadducts were obtained in good yields (81–89%) with high regio- and stereoselectivity. The results are summarized in Table 1.

In conclusion, we have developed a method for the synthesis of a variety of chromeno[4,3-*b*]pyrroles by intramolecular 1,3-dipolar cycloaddition using Baylis–Hillman adducts as dipolarophiles. We found that the reaction can be more efficiently carried out to give good yields of products in short reaction times under ultrasonic irradiation.

Acknowledgements

E.R. thanks CSIR, New Delhi, for fellowships. R.R. thanks DST, DST-FIST for financial assistance.

References and notes

1. Vedejs, E.; Piotrowski, D. W.; Tucci, F. C. *J. Org. Chem.* **2000**, *65*, 5498–5505.
2. Pandey, G.; Sahoo, A. K.; Bagul, T. D. *Org. Lett.* **2000**, *2*, 2299–2301.
3. Vedejs, E.; Klapers, A.; Naidu, B. N.; Piotrowski, D. W.; Tucci, F. C. *J. Am. Chem. Soc.* **2000**, *122*, 5401–5404.
4. Coldham, I.; Crapnell, K. M.; Moseley, J. D.; Rabot, R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1758–1764.
5. Novikov, M. S.; Khlebnikov, A. F.; Besidina, O. V.; Kastikov, R. R. *Tetrahedron Lett.* **2001**, *42*, 533–535.
6. Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891.
7. Ciganek, E.. In *Organic Reactions*; Wiley: New York, 1997; Vol. 51, p 201.
8. Drewes, S. E.; Emslie, N. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2079–2083.
9. Roush, W. R.; Brown, B. B. *J. Org. Chem.* **1993**, *58*, 2151.
10. Jenn, T.; Heissler, D. *Tetrahedron* **1998**, *54*, 97–106.
11. Grassi, D.; Lippuner, V.; Aebi, M.; Brunner, J.; Vasella, A. *J. Am. Chem. Soc.* **1997**, *119*, 10992–10999.
12. Hoffmann, H. M. R.; Rabe, J. *J. Org. Chem.* **1985**, *50*, 3849–3859.
13. Moiseenkov, A. M.; Cheskis, B. A.; Shapiro, N. A.; Stashina, G. A.; Zhulin, V. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1990**, *39*, 517–521.
14. Cheskis, B. A.; Moiseenkov, A. M.; Shapiro, N. A.; Stashina, G. A.; Zhulin, V. M. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1990**, *39*, 716–720.
15. Mateus, C. R.; Feltrin, M. P.; Costa, A. M.; Coelho, F.; Almeida, W. P. *Tetrahedron* **2001**, *57*, 6901–6908.
16. Basavaiah, D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 1253–1258.
17. Morrocchi, S.; Ricca, A.; Velo, L. *Tetrahedron Lett.* **1967**, 331–334.
18. Levna, I. S.; Morticova, E. I.; Kamernitzky, A. V. *Synthesis* **1972**, 562–563.
19. Okuhawa, F.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, *41*, 113–114.
20. Misono, M. *Catal. Rev. Sci. Engl.* **1987**, *29*, 269–272.
21. Kozhevnikov, I. V. *Catal. Rev. Sci. Engl.* **1995**, *37*, 311–352.
22. Poornachandran, M.; Raghunathan, R. *Tetrahedron Lett.* **2005**, *46*, 7197–7200.
23. Poornachandran, M.; Raghunathan, R. *Tetrahedron* **2006**, *62*, 11274–11281.
24. Arumugam, N.; Jayashankaran, J.; Rathnadurga, R.; Raghunathan, R. . *Tetrahedron* **2005**, *61*, 8512–8516.
25. Jayashankaran, J.; Rathnadurga, R.; Raghunathan, R. *Tetrahedron Lett.* **2004**, *45*, 7303–7305.
26. Amalraj, A.; Raghunathan, R.; Sridevikumari, M. R.; Raman, N. *Bioorg. Med. Chem.* **2003**, *11*, 407–419.
27. Subramaniyan, G.; Raghunathan, R.; Martin Castro, A. M. *Synthesis* **2002**, 2440–2445.
28. Subramaniyan, G.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 2909–2913.
29. Amalraj, A.; Raghuanthan, R. *Tetrahedron* **2001**, *57*, 10293–10298.
30. Suresh Babu, A. R.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 6809–6813.
31. Ramesh, E.; Kathiresan, K.; Raghunathan, R. *Tetrahedron Lett.* **2007**, *48*, 1835–1839.
32. Buchholz, R.; Hoffmann, H. M. R. *Helv. Chim. Acta.* **1991**, *74*, 1213–1221.
33. *Spectral data for new compounds*: (*Z*)-methyl 2-((2-formylphenoxy)-methyl)-3-(phenyl)acrylate **4a**: IR (KBr) 1715, 1700 cm^{-1}; mp 85 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.85 (s, 3H), 4.99 (s, 2H), 8.09 (s, 1H), 6.96–7.95 (m, 9H), 10.42 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.4, 63.6, 113.3, 121.2, 125.4, 126.6, 127.1, 128.2, 128.6, 128.7, 128.5, 129.8, 134.2 135.8, 146.0, 160.9, 167.3, 189.6. MS (EI) *m/z*: 296.10. Anal. Calcd for $C_{18}H_{16}O_4$: C, 72.97; H, 5.40. Found: C, 72.74; H, 5.45. (*Z*)-methyl 2-((2-formylphenoxy)methyl)-3-(4-chlorophenyl)-acrylate **4b**: IR (KBr) 1719, 1707 cm^{-1}; mp 116 °C; ^1H NMR

(300 MHz, $CDCl_3$): δ 3.79 (s, 3H), 4.88 (s, 2H), 7.19 (s, 1H), 6.96–7.95 (m, 8H), 10.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 52.3, 68.7, 114.8, 121.6, 126.4, 126.4, 127.6, 128.7, 128.7, 128.0, 130.9, 133.6, 135.2, 135.6, 137.0, 161.2, 167.2, 191.0. MS (EI) $m/z = 330.07$ Anal. Calcd for $C_{18}H_{15}ClO_4$: C, 65.36; H, 4.57; Cl, 10.72. Found: C, 65.13; H, 4.59; Cl, 10.65.

34. Typical procedure: *Method A*: A solution of (*Z*)-methyl 2-((2-formylphenoxy)methyl)-3-(phenyl)acrylate (1 mmol) and sarcosine (1 mmol), in anhydrous methanol (10 ml), was refluxed. Completion of the reaction was evidenced by TLC analysis. The solvent was removed under vacuum. The crude product was subjected to column chromatography on silica gel (100–200 mesh) using petroleum ether–ethyl acetate (7:3) as the eluent. *Method B*: A mixture of (*Z*)-methyl 2-((2-formylphenoxy)methyl)-3-(phenyl)acrylate (1 mmol), sarcosine (1 mmol), and anhydrous methanol (10 ml), at room temperature was irradiated by ultrasound until the disappearance of the starting materials (1 h, monitored by TLC). After standing for 1 h, the reaction mixture was concentrated under vacuum and the crude mixture was purified by column chromatography to afford the pure product. Methyl 3-(phenyl)-1,2,3,3a,4,9b-hexahydro-1-methylchromeno-[4,3-*b*]pyrrole-3a-carboxylate **5a**: IR (KBr): 1706 cm^{-1}; mp 122 °C; ^1H NMR (300 MHz, $CDCl_3$): 2.53 (s, 3H, –NMe), 2.95 (dd, 1H, $J = 9.9$, 5.4 Hz), 3.38 (dd, 1H, $J = 3.3$, 9.9 Hz), 3.63 (d, 1H, $–OCH_2$, $J = 10.8$ Hz), 3.67 (s, 1H,), 3.67 (s, 3H, $–COOCH_3$), 3.75 (dd, 1H, benzylic H, $J = 3.3$, 5.4 Hz), 4.02 (d, $J = 10.8$ Hz, 1H, OCH_2), 6.81–7.343 (m, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 39.7, 48.52, 52.0, 52.3, 60.8, 65.8, 67.0, 76.7, 116.9, 119.7, 120.0,127.2, 128.2, 128.83, 129.0, 131.3, 138.0, 154.4, 173.8. MS (EI) $m/z = 323.15$ (M^+) Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.30; H, 6.50; N, 4.33. Found: C, 73.83; H, 6.55; N, 4.38. Methyl 3-(4-chlorophenyl)-1,2,3,3a,4,9b-hexahydro-1-methylchromeno[4,3-*b*]pyrrole-3a-carboxylate **5b**: IR (KBr): 1706 cm^{-1}; mp 210 °C; ^1H NMR (300 MHz, $CDCl_3$): 2.51 (s, 3H, –NMe), 2.85 (dd, 1H, $J = 9.3$, 5.6 Hz), 3.38 (dd, 1H, $J = 3.3$, 9.3 Hz), 3.63 (d, 1H, $–OCH_2$, $J = 10.8$ Hz), 3.67 (s, 1H,), 3.62 (s, 3H, $–COOCH_3$), 3.65 (dd, 1H, benzylic H, $J = 3.3$, 5.6 Hz), 4.02 (d, $J = 10.8$ Hz, 1H, OCH_2), 6.81–7.343 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 39.7, 47.7, 52.9, 52.4, 60.7, 65.6, 67.0, 76.7, 116.9, 119.4, 120.1, 128.4, 130.2, 131.3, 133.3, 133.0, 136.6, 154.6, 173.6 ppm; MS (EI) *m/z*: 357.83 (M^+) Anal. Calcd for $C_{20}H_{20}ClNO_3$: C, 67.13; H, 5.63; N, 3.91; Cl, 9.91. Found: C, 67.30; H, 5.74; N, 3.88; Cl, 9.85.

35. Shengjun Luo, S.; Fang, F.; Zhao, M.; Zhai, H. *Tetrahedron* **2004**, *60*, 5353–5355.
36. Confalone, P. N.; Huie, E. M. *J. Am. Chem. Soc.* **1984**, *106*, 7175–7178.
37. The crystal structure of **5b** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 651813.