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Hetero [6+3] Cycloaddition of Fulvenes with *N*-Alkylidene Glycine Esters: A Facile Synthesis of the Delavayine and Incarvillateine Framework

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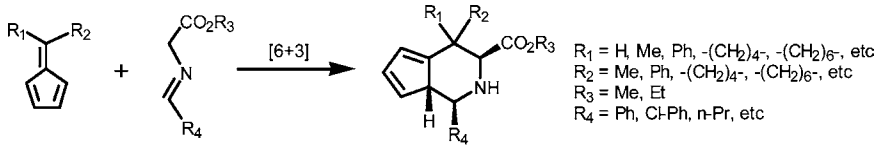
ABSTRACT



In contrast to the [3+2] or [4+3] cycloaddition of *N*-metalated azomethine ylides and various alkenes, *N*-benzylidene glycine ethyl ester reacts with fulvenes to give the hetero [6+3] cycloaddition adducts with high stereoselectivity, constituting an efficient and novel route to [2]-pyrindines.

The theoretical, mechanistic, and synthetic importance of fulvene and its derivatives have intrigued chemists for more than a century.[1] Cycloadditions of fulvenes (e.g. [4+3],[2] [2+2],[3] [4+2],[4] [2+4],[5] [6+4],[6] [6+2][7]) provide versatile and powerful approaches to various polycyclic systems and natural products. Recently, we reported a new type of reaction: the [6+3] cycloaddition of fulvenes[8] for the facile synthesis of indan derivatives.[9] More recently, Barluenga et al. demonstrated that the [6+3] cycloaddition of chromium alkenyl carbene complexes with fulvene leads to indanes.[10] Additionally, we recently reported a novel hetero [6+3] cycloaddition of fulvenes for the synthesis of 11-oxa-steroids.[11] In conjunction with our continuing efforts in fulvene chemistry,[12] we have now developed a hetero [6+3] cycloaddition of fulvenes and *N*-benzylidene glycine ethyl ester that yields [2]pyrindines. To the best of our knowledge,

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(1) For a recent review on fulvene chemistry, see: Neuenschwander, M. In *Chemistry of Double-Bonded Functional Groups*; Patai, S., Ed.; Wiley: Chichester, UK, 1989; Vol. 2, p 1131.

(2) (a) Rawson, D. I.; Carpenter, B. K.; Hoffmann, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1786. (b) Noyori, R.; Hayakawa, Y.; Takaya, H.; Murai, S.; Kobayashi, R.; Sonoda, N. *J. Am. Chem. Soc.* **1978**, *100*, 1759.

(3) Imafuku, K.; Arai, K. *Synthesis* **1989**, 501. Paquette, L. A.; Colapret, J. A.; Andrews, D. R. *J. Org. Chem.* **1985**, *50*, 201.

(4) (a) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480. (b) Gleiter, R.; Borzyk, O. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1001.

(5) (a) Himeda, Y.; Yamataka, H.; Ueda, I.; Hatanaka, M. *J. Org. Chem.* **1997**, *62*, 6529. (b) Nair, V.; Nair, A. G.; Radhakrishnan, K. V.; Nadakumar, M. V.; Rath, N. P. *Synlett* **1997**, 767.

(6) (a) Gupta, Y. N.; Doa, M. J.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7336−7338. (b) Yoshida, Z.-I.; Shibata,M.; Ogino, E.; Sugimoto, T. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 60.

(7) (a) For an example of intermolecular [6+2] cycloaddition, see: Hong, B. C.; Shr, Y. J.; Wu, J. L.; Gupta, A. K.; Lin, K. J. *Org. Lett.* **2002**, *4*, 2249−2252. (b) For an example of intramolecular [6+2] cycloaddition, see: Suda, M.; Hafner, K. *Tetrahedron Lett.* **1977**, 2453. Wu, T. C.; Houk, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 5308.

(8) Hong, B.-C.; Sun, S.-S.; Tsai, Y.-C. *J. Org. Chem.* **1997**, *62*, 7717.

(9) For a recent review on the synthesis of indan systems, see: Hong, B.-C.; Sarshar, S. *Org. Prep. Proced. Int.* **1999**, *31*, 1.

(10) Barluenga, J.; Martinez, S.; Suárez-Sobrino, A. L.; Tomás, M. *J. Am. Chem. Soc.* **2001**, *123*, 11113−11114.

(11) Hong, B.-C.; Chen, Z.-Y.; Chen, W.-H. *Org. Lett.* **2000**, *2*, 2647−2649.

(12) For previous papers in this series, see: (a) Hong, B.-C.; Shr, Y.-J.; Liao, J.-H. *Org. Lett.* **2002**, *4*, 663−666. (b) Hong, B.-C.; Shen, I.-C.; Liao, J.-H. *Tetrahedron Lett.* **2001**, *42*, 935−938. (c) Hong, B.-C.; Jiang, Y.-F.; Kumar, E. S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1981−1984. (d) Hong,

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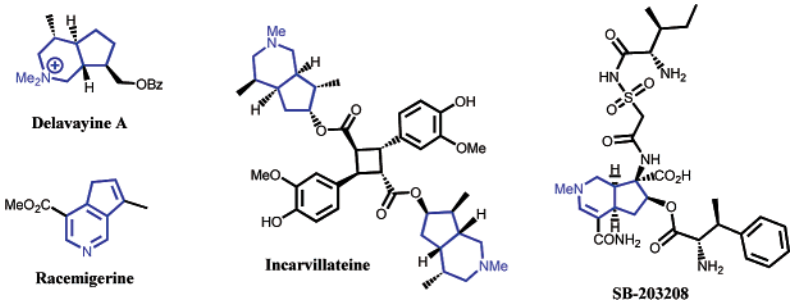
Scheme 1



the synthesis of [2]pyrindines via a hetero [6+3] cycloaddition has never been reported. [2]Pyrindine systems can be found in a variety of natural products including delavayine A,[13] SB-203208,[14] incarvillateine,[15] louisianin A,[16] and racemigerine[17] (Scheme 1).[18] The 1,3-dipolar cycloaddition of *N*-alkyl glycine ester to alkenes via a [3+2] pathway[19] or with a diene via a [4+3] pathway[20] represents an efficient and convergent approach to pharmacologically active alkaloids (e.g. the synthesis of pyrrolidines[21] via the [3+2] cycloaddition reaction of azomethine ylides[22] and alkenes). The 1,3-dipolar cycloaddition of fulvene has received much less attention, but examples of the [6+4], [4+2], and [3+2] cycloadditions of fulvene have been reported.[23−25]

On the basis of our previous observations, we suspected that the addition of a heterodipolar reagent, such as an azomethine ylide, to fulvene could afford the hetero [6+3] cycloadduct and provide a novel route to the [2]pyrindine skeleton. In a model study, we have found that the *N*-benzylidene glycine ethyl ester derived from benzaldehyde and glycine ethyl ester in the presence of LDA in dry THF reacts with 6,6-dimethylfulvene (**1**) to yield the predicted hetero [6+3] cycloadduct **4** as the only isolable product in 80% yield (Scheme 2). The structure of **4** was assigned based on IR, ^{1}H, ^{13}C NMR, COSY, DEPT, HMQC, HMBC, MS, and HRMS analysis. The formation of **4** may be rationalized via the stepwise mechanism shown in Scheme 2. Initial addition of the metalloazomethine ylide **2** to the C-6 position of fulvene **1** generates the zwitterionic intermediate **3**. This is followed by cyclization to give the [2]pyrindine **4**. The chairlike transition state places the alkyl substituents at the equatorial positions throughout the cyclization process and leads to the formation of adduct **4** with high stereoselectivity. The azomethine ylides were generated by using a variety of methods (Table 1, entry 1, methods B−F). Among these, method D (Ag_2O in Et_3N−THF) gave the highest yield (92%) along with 8% of the uncyclized imine.

A series of homologous metalloazomethine ylides were then reacted with various fulvenes to afford the corresponding products **6**, **8**, **10**, and **12** (entries 2−5, Table 1).[26] The structure of **8** was unambiguously assigned by single-crystal X-ray analysis (Figure 1).[27] The reaction of various monoalkylfulvenes with metalloazomethine ylides gave similar adducts **14**, **17** and **15**, **18** in a 1:1 ratio of stereoisomers, respectively (entries 6−7, Table 1). The structure of **14** was also unambiguously assigned by single-crystal X-ray analysis (Figure 1).[28]

B.-C.; Sun, H.-I.; Chen, Z.-Y. *Chem. Commun.* **1999**, 2125. (e) Hong, B.-C.; Chen, Z.-Y.; Kumar, E. S. *J. Chem. Soc, Perkin Trans. 1* **1999**, 1135. (f) Hong, B.-C.; Hong, J.-H. *Tetrahedron Lett.* **1997**, *38*, 255. (g) Hong, B.-C.; Sun, S.-S.; Tsai, Y.-C. *J. Org. Chem.* **1997**, *62*, 7717.

(13) Nakamura, M.; Kido, K.; Kinjo, J.; Nohara, T. *Phytochemistry* **2000**, *53*, 253−256.

(14) Stefanska, A. L.; Cassels, R.; Ready, S. J.; Warr, S. R. *J. Antibiot.* **2000**, *53*, 357−363.

(15) Nakamura, M.; Chi, Y.-M.; Yan, W.-M.; Yonezawa, A.; Nakasugi, Yumiko; Y., Toyokichi; Hashimoto, F.; Kinjo, J.; Nohara, T.; Sakurada, S. *Planta Med.* **2001**, *67*, 114−117.

(16) Sunazuka, T.; Zhi-Ming, T.; Harigaya, Y.; Takamatsu, S.; Hayashi, M. *J. Antibiot.* **1997**, *50*, 274−275.

(17) Skaltsounis, A.-L.; Michel, S.; Tillequin, F.; Koch, M.; Pusset, J.; Chauviere, G. *Helv. Chim. Acta* **1985**, *68*, 1679−1685.

(18) (a) Cook, C. E.; Wani, M. C.; Jump, J. M.; Lee, Y.-W.; Fail, P. A. *J. Med. Chem.* **1995**, *38*, 753−763. (b) Jump, J. M.; McPhail, A. T.; Cook, C. E. *Tetrahedron Lett.* **1997**, *38*, 3691−3694.

(19) The method represents an efficient and convergent method for the construction of the pyrrolidine structure unit, see: (a) Wilson, N. S.; Sarko, C. R.; Roth, G. P. *Tetrahedron Lett.* **2001**, *42*, 8939−8942. (b) Abellán, T.; Mancheño, B.; Nájera, C.; Sansano, J. *Tetrahedron* **2001**, *57*, 6627−6640. (c) Casas, J.; Grigg, R.; Najera, C.; Sansano, J. M. *Eur. J. Org. Chem.* **2001**, *10*, 1971−1982. (d) Subramaniyan, G.; Raghunathan, R. *Tetrahedron* **2001**, *57*, 2909−2916. (e) Grigg, R.; Liu, A.; Shaw, D.; Suganthan, S.; Washington, M. L.; Woodall, D. E.; Yoganathan, G. *Tetrahedron Lett.* **2000**, *41*, 7129−7134. (f) Nyerges, M.; Fejes, I.; Toeke, L. *Tetrahedron Lett.* **2000**, *41*, 7951−7954. (g) Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossio, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078−6092. (h) Dondas, H. A.; Duraisingham, J.; Grigg, R.; MacLachlan, W. S.; MacPherson, D. T.; Thornton-Pett, M.; Sridharan, V.; Suganthan, S. *Tetrahedron* **2000**, *56*, 4063−4070. (i) Fejes, I.; Toke, L.; Nyerges, M.; Pak, C. S. *Tetrahedron* **2000**, *56*, 639−644. (j) Fejes, I.; Toke, L.; Blasko, G.; Nyerges, M.; Pak, C. S. *Tetrahedron* **2000**, *56*, 8545−8554. (k) Gong, Y.-D.; Najdi, S.; Olmstead, M. M.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 3081−3086. (l) Pejes, I.; Nyerges, M.; Szoellosy, A.; Blasko, G.; Toke, L. *Tetrahedron* **2001**, *57*, 1129−1138. (m) Nyerges, M.; Gajdics, L.; Szoelloesy, A.; Toeke, L. *Synlett* **1999**, *1*, 111−113.

(20) (a) Dimroth, F. *Chem. Ber.* **1957**, *90*, 1628−1633. (b) Dallacker, F. *Justus Liebigs Ann. Chem.* **1961**, *643*, 82−90. (c) Waly, M. A. *Boll. Chim. Farm.* **2000**, *139*, 217−221.

(21) Dell, C. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3873−3905.

(22) For a review on *N*-metalated azomethine ylides, see: Kanemasa, S.; Tsuge, O. *Adv. Cycloaddit.* **1993**, *3*, 99−159.

(23) Kato, H.; Kobayashi, T.; Ciobanu, M. *Tetrahedron* **1997**, *53*, 9921−9934.

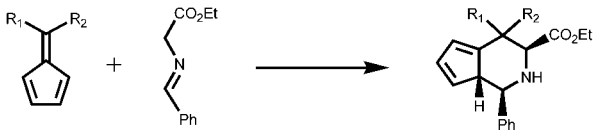
(24) Djapa, F.; Ciamala, K.; Melot, J.-M.; Vebrel, J.; Herlem, G. *J. Chem. Soc., Perkin Trans. 1* **2002**, 687−695.

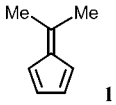
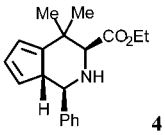
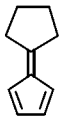
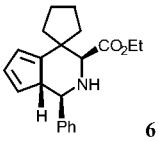
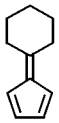
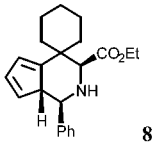
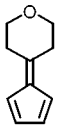
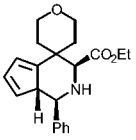
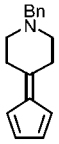
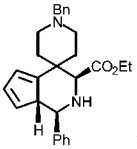
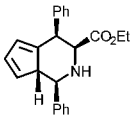
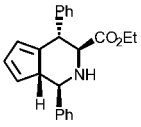
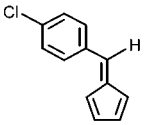
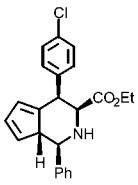
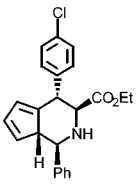
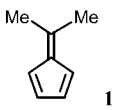
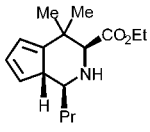
(25) Nair, V.; Nandakumar, M. V.; Maliakal, D.; Mathen, J. S.; Rath, N. P. *Tetrahedron* **2000**, *56*, 8001−8005.

(26) All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, DEPT, IR, MS, and HRMS. In most cases COSY and HMQC spectra were also obtained. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

(27) Crystallographic data for **8**: $C_{22}H_{27}NO_2$, M = 337.45, monoclinic, space group $P2_1/c$, T = 295 K, a = 8.2285(1) Å, b = 23.0207(4) Å, c = 10.2019(2) Å, β = 99.0300(6)°, V = 1908.55(6) Å^3, Z = 4, D = 1.174 g/cm^3, λ (Mo $K\alpha$) = *0.71073* Å, 13582 reflections collected, 4381 unique reflections, 227 parameters refined on F^2, R = 0.0669, $wR2[F^2]$ = 0.1773 [2341 data with $F^2 > 2\sigma(F^2)$].

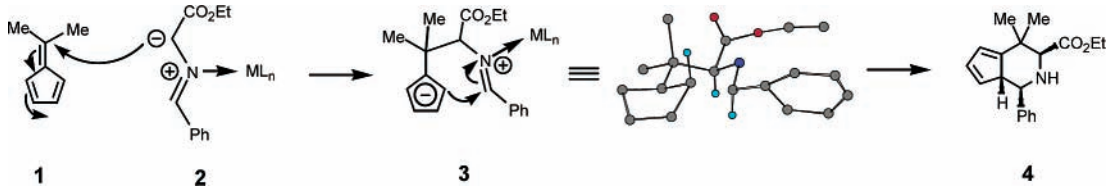
Table 1. Reaction of *N*-Alkylidene Glycine Ester with Fulvenes



entry	fulvene	product	method	time (h)	yield (%)[a]
1	 **1**	 **4**	A	1	80
			B	24	75
			C	24	20
			D	12	92[b]
			E	12.5	7[c]
			F	4	53[d]
			G	6 for step 1 4 for step 2	75[b]
2	 **5**	 **6**	A	1	57
			D	12	70[b]
3	 **7**	 **8**	A	1	73
			D	12	86[b]
4	 **9**	 **10**	A	1	66
			D	12	78[b]
5	 **11**	 **12**	A	1	75
			D	12	89[b]
6	 **13**	 **14**  **15** (1:1)	A	1	71
			D	12	63[b]
7	 **16**	 **17**  **18** (1:1)	A	1	74
			D	12	68[b]
8	 **1**	 **19**	G	6 for step 1 4 for step 2	67[e,f]

[a] Isolated yield based on starting fulvene. Method A: LDA, THF, −78 °C. Method B: LiBr, Et_3N, THF, 25 °C. Method C: toluene, reflux. Method D: Ag_2O, Et_3N, THF, 25 °C. Method E: LiBr, DBU, 25 °C. Method F: AgOAc, Et_3N, 25 °C. Method G: glycine ethyl ester, C_6H_5CHO, $MgSO_4$, toluene, reflux, 12 h; fulvene **1**, Ag_2O, Et_3N, 25 °C, 12 h. [b] 8% of the uncyclized imine was obtained. [c] 90% of the uncyclized imine was obtained. [d] 47% of the uncyclized imine was obtained. [e] Reacted with *N*-propyl glycine ethyl ester hydrochloride. [f] Total yield for two steps.

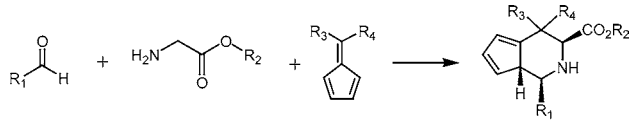
Scheme 2



1 2 3 4

The two-step reaction can be carried out in one pot by heating a 64 mM solution of benzaldehyde (1 equiv), glycine ethyl ester hydrochloride (1.3 equiv), Et_3N (5 equiv), and $MgSO_4$ in toluene to reflux for 6 h, followed by addition of a THF solution of fulvene **1** (1.2 equiv), Et_3N, and Ag_2O at ambient temperature and stirring for 4 h (Table 1, entry 1, method G, Table 1). This process yields adduct **4** in 75% yield without the need for isolation of the *N*-alkylidene glycine ester.

Scheme 3

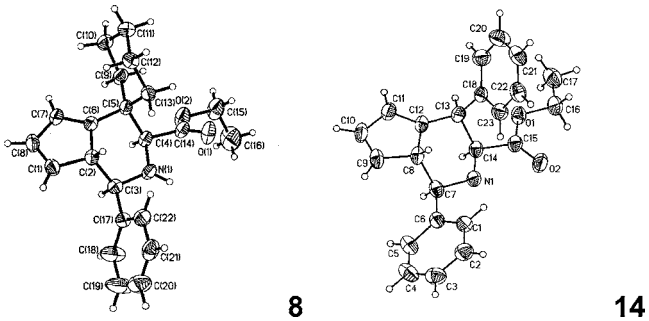


$R_1 = C_6H_5$, *p*-ClC_6H_4, *p*-$OMeC_6H_4$, C_3H_7, *c*-C_6H_{11};
R_2 = Me, Et; R_3 = Me, -$(CH_2)_5$-, Ph; R_4= -$(CH_2)_5$-, H

Next a selection of 3 fulvenes, 2 glycine esters, and 5 aldehydes were reacted according to Method G to yield a 30-membered [2]pyrindine library. During this process, heating in toluene was maintained for 12 h and the cyclization was allowed to proceed at ambient temperature for 8 h. Simple filtration through Celite and removal of the solvent afforded the final products in good yield and pure enough for MS and/or NMR analysis without further purification.

(28) Crystallographic data for **14**: $C_{23}H_{23}NO_2$, M = 345.42, monoclinic, space group $P2_1/c$, T = 295 K, a = 11.0990(9) Å, b = 8.6516(7) Å, c = 20.1131(16) Å, β = 101.3730(10)°, V = 1893.4(3) Å^3, Z = 4, D = 1.212 g/cm^3, λ (Mo $K\alpha$) = 0.71073 Å, 8110 reflections collected, 2732 unique reflections, 237 parameters refined on F^2, R = 0.0473, $wR2[F^2]$ = 0.1338 [2339 data with $F^2 > 2\sigma(F^2)$].

In summary, we have developed a novel synthesis of [2]-pyrindine derivatives (delavayine and incarvillateine skeletons) via a stereoselective one-pot hetero [6+3] cycloaddition of *N*-alkylidene glycine esters to fulvenes. We are currently pursuing the application of this methodology to the solid-phase synthesis of a large [2]pyrindine library and other natural products.



8 **14**

Figure 1. ORTEP plots for X-ray crystal structures of **8** and **14**.

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Supporting Information Available: Crystallographic information files (CIF) for **8** and **14** and experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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