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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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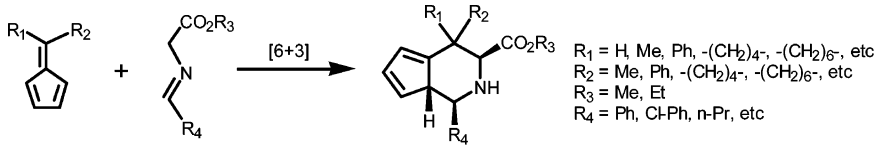
ABSTRACT



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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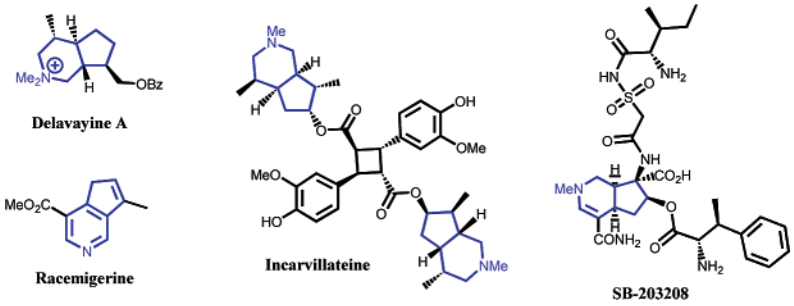
Scheme 1



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]

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(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.

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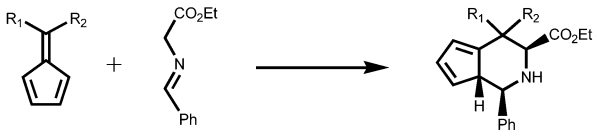
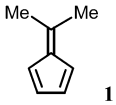
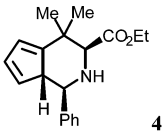
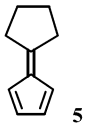
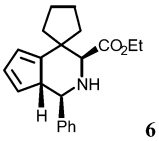
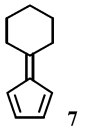
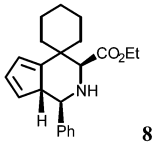
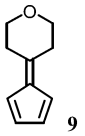
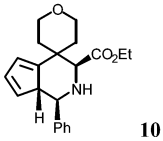
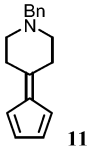
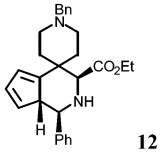
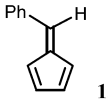
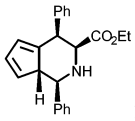
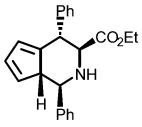
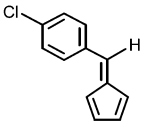
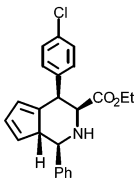
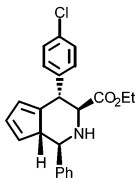
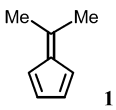
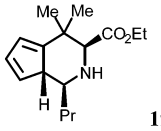
(26) All new compounds were fully characterized by ^{1}H NMR, ^{13}C NMR, DEPT, IR, MS, and HRMS. In most cases COSY and HMQC spectra were also obtained. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials.

(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 $F^2 > 2\sigma(F^2)$].

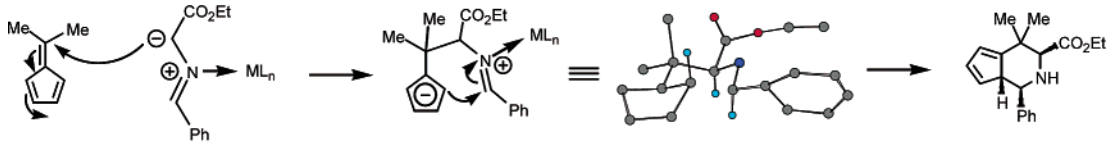
Table 1. Reaction of *N*-Alkylidene Glycine Ester with Fulvenes



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.

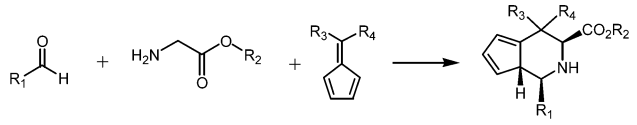
Scheme 2



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

Scheme 3



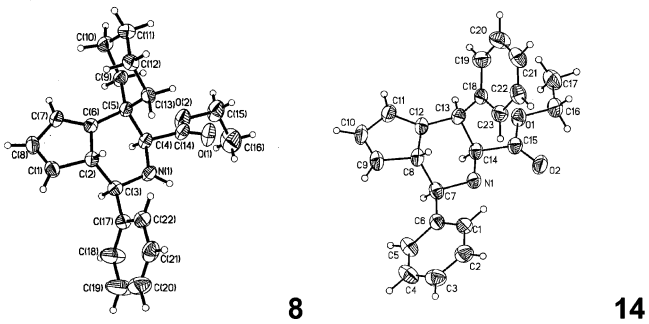
R_1 = C_6H_5, *p*-ClC_6H_4, *p*-$OMeC_6H_4$, C_3H_7, *c*-C_6H_{11};
R_2 = Me, Et; R_3 = Me, -$(CH_2)_5$-, Ph; R_4= -$(CH_2)_5$-, H

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.

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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