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Formal [6+3] cycloaddition of fulvenes with 2*H*-azirine: a facile approach to the [2]pyrindines system ☆

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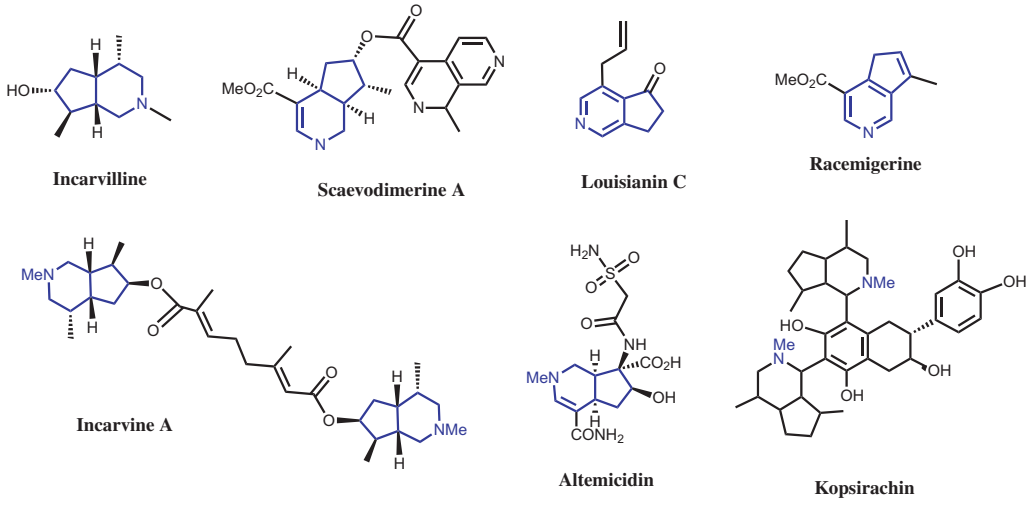
Abstract—2*H*-Azirine reacts with fulvenes to give either alkylated fulvene azirines (ultrasound) or the formal [6+3] cycloaddition adducts (Lewis acid). The later constitutes an efficient and novel route to [2]pyrindines.

The theoretical, mechanistic, and synthetic importance of fulvene and its derivatives has 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 indane 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 the novel hetero [6+3] cycloaddition of fulvenes for the synthesis of 11-oxasteroids[11] and hetero [6+3] cycloaddition of fulvenes with *N*-alkylidene glycine esters.[12] In conjunction with our continuing efforts in fulvene chemistry,[13] we have now developed a formal [6+3] cycloaddition of fulvenes and 2*H*-azirine that yields [2]pyrindines. [2]Pyrindine systems can be found in a variety of natural products including incarvilline,[14] incarvine A,[15] scaevodimerine A,[16] louisianin C,[17] altemicidin[18], racemigerine,[19] kopsirachin,[20] (Scheme 1).



Scheme 1.

Keywords: Cycloaddition; Fulvene; Azirine; Pyrindines.
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The cycloaddition and regioselective ring cleavage of 2*H*-azirines is known to give rise to reactive species such as vinylnitrenes, iminocarbenes, and nitrile ylides.[21] These versatile 2*H*-azirines can act as nucleophiles, electrophiles, dienophiles, and dipolarophiles in cycloadditions. Yet the cycloaddition of 2*H*-azirines with polyenes has received little attention; only one example of a [6+3] cycloaddition of cycloheptatriene and 2*H*-azirine has been reported.[22]

We suspected that the addition of 2*H*-azirine to fulvene would afford the hetero [6+3] cycloadduct and provide a novel route to the [2]pyrindine skeleton. The azirines were prepared from the corresponding methyl-1-azido cinnamates (heptane, heat, 2–4 h),[23] and the crude product was used without further purification. In a model study, dimethyl fulvene (**1a**) and crude azirine **2** were stirred in dry THF for 3 days to afford [2]pyrindine **4a** as the only isolable product (19% yield) and recovered starting fulvene. The yield of **4a** was improved to 83% in the presence of 20 mol% of $Y(OTf)_3$ in THF. The structure of **4a** was assigned based on IR, ^1H, ^{13}C NMR, COSY, DEPT, HMQC HMBC, MS, and HRMS analysis. [2]Pyrindine **4a** proved unstable and gradually converted to **5a** after a few days in the refrigerator. This isomerization is accelerated in the presence of Et_3N in CH_2Cl_2 at ambient temperature. The formation of **4a** maybe rationalized via the stepwise mechanism shown in Scheme 2. Initial addition of the fulvene to the activated 2*H*-azirine generates the zwitterionic intermediate, which cyclizes to [2]pyrindine **4a**. Unlike the typical concerted 1,3-dipolar reaction of *N*-alkylidene glycine ester with fulvenes,[12] the addition of 2*H*-azirines to fulvenes occurs most likely via a stepwise mechanism. Such behavior is a direct result of the ambient nature of 2*H*-azirines, and can be attributed to the high ring strain, reactive π-bond and the nitrogen lone pair. On the other hand, reaction of fulvene **1a** and azirine **2** in an ultrasonic bath (neat, RT, 2 days) yielded the alkylation product **3a**. Although unexpected and unprecedented, it is possible that the initial Diels–Alder adduct of **1a** and **2** rearranges to give **3a** (Scheme 3). The structure of **3a** was unambiguously assigned by the single crystal X-ray analysis of its DIBAL-H reduction product **6** (Fig. 1).[24]

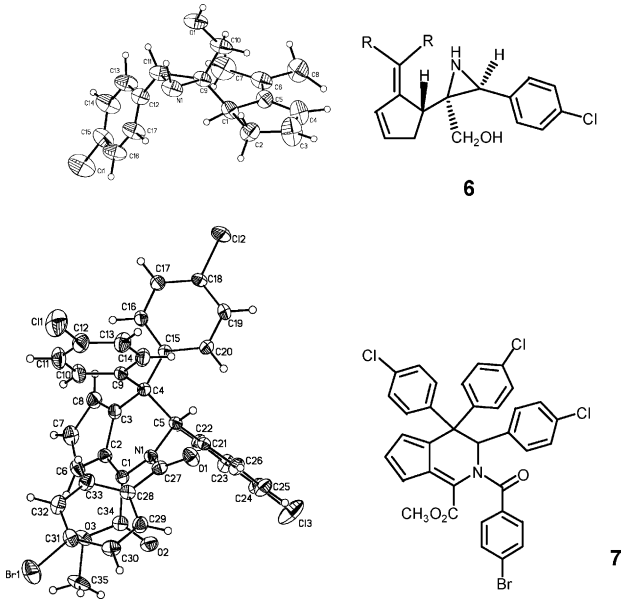
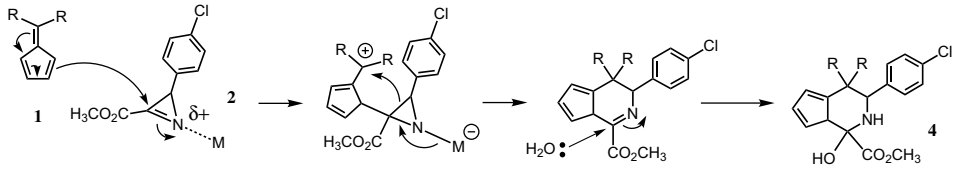
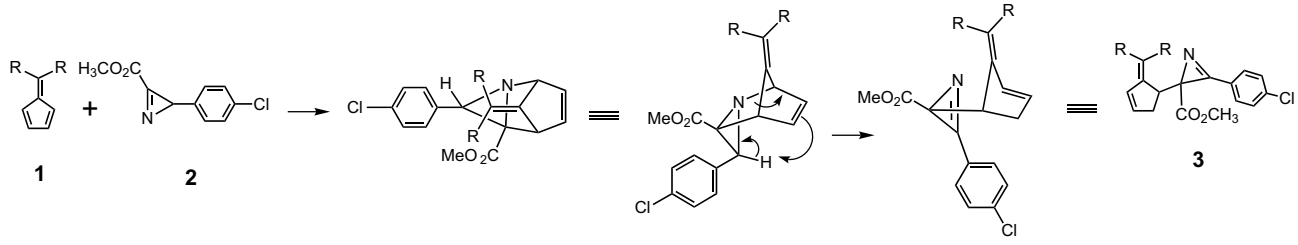


Figure 1. ORTEP plots for X-ray crystal structures of **6** and **7**.

A series of homologous fulvenes were then reacted with 2*H*-azirine to afford the corresponding [2]pyrindines, (entries 2–7, Table 1).[25] Interestingly, fulvenes **1e** and **1f** afforded **4** as the only product regardless of the method used. The structure of **5f** was unambiguously assigned by the single crystal X-ray analysis of its *p*-bromobenzoate derivative **7** (Fig. 1).[26] The two-step transformation of **1** to **5** can be carried out in one-pot by addition of excess of Et_3N after formation of adduct **4**. Reaction of monosubstituted fulvene **1g** with 2*H*-azirine gave **4g** in 85% (Method C), which gave **5g** in THF at ambient temperature for 36 h (Method E). **5g** was

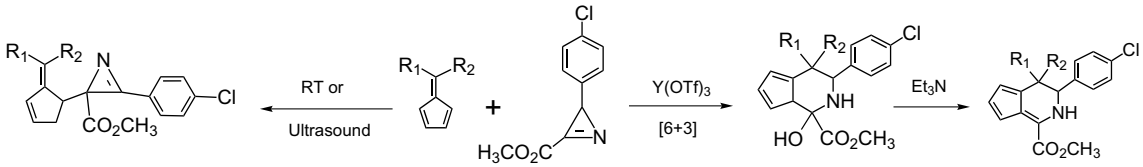


Scheme 2.

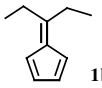
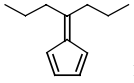
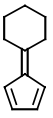
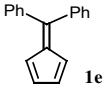
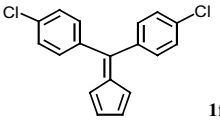
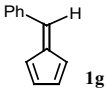


Scheme 3.

Table 1. Reaction of fulvenes with 2*H*-azirines

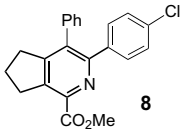


3 **1** **2** **4** **5**

Entry	Fulvene	Product	Method	Time (h)	Yield (%)[a]
1	 **1a**	$R_1 = R_2 =$ Me, **4a**	A	72	19[b]
		$R_1 = R_2 =$ Me, **3a**	B	48	75[c]
		$R_1 = R_2 =$ Me, **4a**	C	12	83[d]
		$R_1 = R_2 =$ Me, **5a**	D	0.5	100
2	 **1b**	$R_1 = R_2 =$ Et, **3b**	A	72	15[b]
		$R_1 = R_2 =$ Et, **3b**	B	48	62[c]
		$R_1 = R_2 =$ Et, **4b**	C	12	68[d]
		$R_1 = R_2 =$ Et, **5b**	D	0.25	100
3	 **1c**	$R_1 = R_2 = C_3H_7$, **3c**	A	72	23[b]
		$R_1 = R_2 = C_3H_7$, **3c**	B	48	71[c]
		$R_1 = R_2 = C_3H_7$, **4c**	C	12	74[d]
		$R_1 = R_2 = C_3H_7$, **5c**	D	0.5	100
4	 **1d**	$R_1 = R_2 = -(CH_2)_{5-}$, **3d**	A	72	27[b]
		$R_1 = R_2 = -(CH_2)_{5-}$, **3d**	B	48	75[c]
		$R_1 = R_2 = -(CH_2)_{5-}$, **4d**	C	12	80[d]
		$R_1 = R_2 = -(CH_2)_{5-}$, **5d**	D	0.5	100
5	 **1e**	$R_1 = R_2 =$ Ph, **4e**	A	72	35[b]
		$R_1 = R_2 =$ Ph, **4e**	B	120	*N.R.*
		$R_1 = R_2 =$ Ph, **4e**	C	12	85[d]
		$R_1 = R_2 =$ Ph, **5e**	D	0.25	100
6	 **1f**	$R_1 = R_2 = p$-ClC_6H_4, **4f**	A	72	23[b]
		$R_1 = R_2 = p$-ClC_6H_4, **4f**	B	120	*N.R*
		$R_1 = R_2 = p$-ClC_6H_4, **4f**	C	12	85[d]
		$R_1 = R_2 = p$-ClC_6H_4, **5f**	D	0.5	100
7	 **1g**	$R_1 =$ H, $R_2 =$ Ph, **3g**:**4g** (4:1)	A	72	30[b]
		$R_1 =$ H, $R_2 =$ Ph, **3g**:**4g** (4:1)	B	72	32[b]
		$R_1 =$ H, $R_2 =$ Ph, **4g**	C	12	85[d]
		$R_1 =$ H, $R_2 =$ Ph, **5g**	E	36	93
		$R_1 =$ H, $R_2 =$ Ph, **8**	F	36	85

[a] Isolated yield based on starting azirine.
[b] Only isolated product, fulvene SM was recovered. The 2*H*-azirine decomposed and prolonged reaction time did not increase the yield.
[c] No **4** was observed.
[d] No **3** was observed. Method A: THF, 25 °C. Method B: neat, ultrasound, 25 °C. Method C: 20 mol% $Y(OTf)_3$, THF, 25 °C. Method D: start from **4**, Et_3N, CH_2Cl_2, 25 °C. Method E: start from **4**, THF, 25 °C. Method F: start from **5**, Et_3N, CH_2Cl_2, 25 °C.

converted to **8** after reaction with Et_3N in CH_2Cl_2 (Method F).



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In summary, we have developed a novel synthesis of [2]pyrindine derivatives via a regioselective one-pot hetero [6+3] cycloaddition of 2*H*-azirine 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.

Acknowledgements

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24. Crystallographic data for **6**: $C_{17}H_{20}ClNO$, $M = 289.79$, monoclinic, space group $P2_1/c$, $T = 298\,K$, $a = 8.925(2)$, $b = 9.141(2)$, $c = 19.223(5)\,Å$, $\beta = 97.949(5)°$, $V = 1553.1(7)\,Å^3$, $Z = 4$, $D = 1.239\,g/cm^3$, λ (Mo-K$_\alpha$) = 0.71073 Å, 9179 reflections collected, 3618 unique reflections, 189 parameters refined on F^2, $R = 0.0623$, $wR_2[F^2] = 0.1143$ [3618 data with $F^2 > 2\sigma(F^2)$].
25. All new compounds were fully characterized by ^1H 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.
26. Compound **7** was prepared from **5f** with *p*-BrC_6H_4COCl, Et_3N, DMAP, CH_2Cl_2; 90% yield. Crystallographic data for **7**: $C_{35}H_{23}BrCl_3NO_3$, $M = 691.80$, monoclinic, space group $P2_1/n$, $T = 298\,K$, $a = 10.1791(7)$, $b = 20.1109(13)$, $c = 15.2109(10)\,Å$, $\beta = 92.063(2)°$, $V = 3111.8(4)\,Å^3$, $Z = 4$, $D = 1.477\,g/cm^3$, λ (Mo-K$_\alpha$) = 0.71073 Å, 19,116 reflections collected, 7267 unique reflections, 389 parameters refined on F^2, $R = 0.0574$, $wR_2[F^2] = 0.1114$ [3612 data with $F^2 > 2\sigma(F^2)$].