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Abstract—2H-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 fulvenes8 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-oxasteroids11 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 2H-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 altemicidin18, racemigerine,19 kopsirachin,20 (Scheme 1).

Scheme 1.
The cycloaddition and regioselective ring cleavage of 2H-azirines is known to give rise to reactive species such as vinylnitrenes, iminocarbenes, and nitrile ylides. These versatile 2H-azirines can act as nucleophiles, electrophiles, dienophiles, and dipolarophiles in cycloadditions. Yet the cycloaddition of 2H-azirines with polyenes has received little attention; only one example of a [6+3] cycloaddition of cycloheptatriene and 2H-azirine has been reported.

We suspected that the addition of 2H-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), and the crude product was used without further purification. In a model study, dimethyl fulvene (1a) and crude azirine 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, 13C 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 Et3N in CH2Cl2 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 2H-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, the addition of 2H-azirines to fulvenes occurs most likely via a stepwise mechanism. Such behavior is a direct result of the ambient nature of 2H-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).

A series of homologous fulvenes were then reacted with 2H-azirine to afford the corresponding [2]pyrindines, (entries 2–7, Table 1). 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-bromo-benzoate derivative 7 (Fig. 1). The two-step transformation of 1 to 5 can be carried out in one-pot by addition of excess of Et3N after formation of adduct 4. Reaction of monosubstituted fulvene 1g with 2H-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.
In summary, we have developed a novel synthesis of 2H-pyridine derivatives via a regioselective one-pot hetero [6+3] cycloaddition of 2H-azirine to fulvenes. We are currently pursuing the application of this methodology to the solid-phase synthesis of a large 2H-pyridine library and other natural products.
Acknowledgements

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References and notes

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


24. Crystallographic data for 6: 2H$_7$H$_2$ClNO, M = 289.79, monoclinic, space group P2$_1$/c, a = 298 K, a = 8.925(2), b = 9.141(2), c = 19.223(5) Å, β = 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$^2$ > 2σ(F$^2$)].

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

26. Compound 7 was prepared from 5f with p-BrC$_6$H$_4$COCl, Et$_3$N, DMAP, CH$_2$Cl$_2$; 90% yield. Crystallographic data for 7: C$_{13}$H$_2$BrCl$_2$NO$_5$, M = 691.80, monoclinic, space group P2$_1$/n, a = 10.1791(7), b = 20.1109(13), c = 15.2109(10) Å, β = 92.063(2)°, V = 31116.8(4) Å$^3$, Z = 4, D = 1.477 g/cm$^3$, λ = (Mo-K$_\alpha$) = 0.71073 Å, 1916 reflections collected, 7267 unique reflections, 389 parameters refined on F$^2$, R = 0.0574, wR$_2$/F$^2$ = 0.1114 [3612 data with F$^2$ > 2σ(F$^2$)].