



## Generation and 1,3-Dipolar Cycloadditions of Fluorine-Containing Azomethine Ylides Derived from Difluorocarbene and Imines

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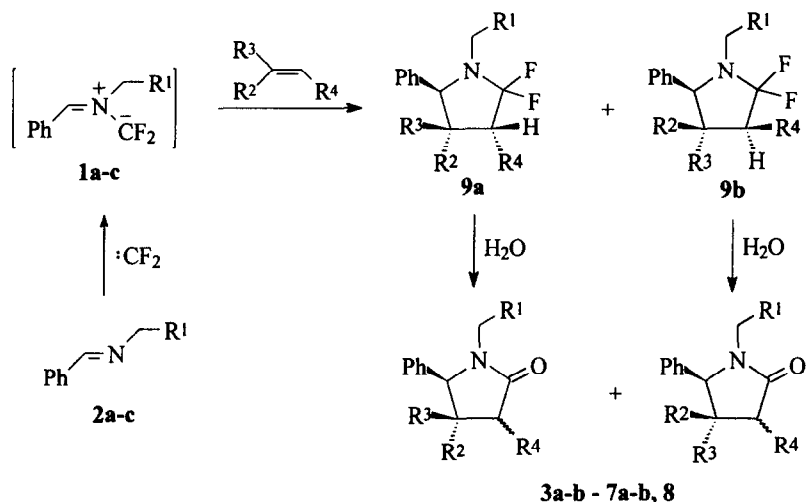
**Abstract:** Iminodifluoromethanides, generated by the reaction of difluorocarbene with N-benzylidene amines, undergo 1,3-dipolar cycloaddition to electron-deficient alkenes to give pyrrolidine derivatives in moderate to good yields. © 1997 Published by Elsevier Science Ltd.

Cycloaddition reactions of azomethine ylides with a carbon-carbon multiple bond are of considerable importance in heterocyclic synthesis.<sup>1</sup> In recent years, much attention from the synthetic standpoint has been paid to reactions proceeding via ylides derived from heteroatomic compounds and carbenes, including dihalogenocarbenes.<sup>2</sup> Thus, 1,3-dipolar cycloaddition of iminodichloromethanides generated by the reaction of dichlorocarbene with C=N bond-containing compounds to alkenes and acetylenes has provided access to a broad spectrum of heterocyclic systems, such as, pyrrole,<sup>3-6</sup> pyridine,<sup>3, 6</sup> pyrrolidine,<sup>7</sup> indolizine,<sup>8</sup> pyrrolidiazine<sup>9</sup> derivatives and others. However, the synthetic utility of dichloromethylides is limited by the low selectivity of dichlorocarbene and the high reactivity of its precursor, trichloromethyl anion, which gives rise to some undesirable reactions.<sup>3, 4</sup>

In this communication, we wish to report on generation and 1,3-dipolar cycloadditions of an unusual type of dihalogen-substituted azomethine ylide, iminodifluoromethanides (**1a-c**), to electron-deficient alkenes.<sup>10</sup> These ylides as well as other ylides from dihalogenocarbenes proved to be labile, so they were generated *in situ* in the presence of alkenes from the corresponding imines and difluorocarbene. The latter was obtained by the reduction of CBr<sub>2</sub>F<sub>2</sub> with lead in the presence of tetrabutylammonium bromide.<sup>11</sup> N-Benzylidene amines (**2a-c**) provided substituted pyrrolidinones (**3-8**) (Table) under the difluorocarbene generation conditions in the presence of but-2-endioic, acrylic and methacrylic acids derivatives followed by chromatographic purification. A typical experimental procedure was as follows. Lead powder (1.2 g, 5.8 mmol), tetrabutylammonium bromide (2.0 g, 6.0 mmol), CH<sub>2</sub>Cl<sub>2</sub> (7 ml), N-benzylidenebenzylamine (**2a**) (0.55 g, 2.7 mmol), dimethyl fumarate (1.00 g, 6.9 mmol), and CBr<sub>2</sub>F<sub>2</sub> (1.92 g, 9.2 mmol) were placed in succession into a tube filled with argon, after which the tube was sealed. The mixture was stirred by rotation or shaking at 45°C until the lead was consumed completely (15 h). The

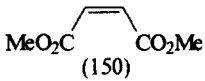
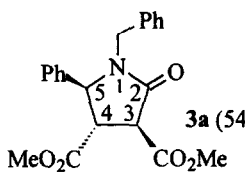
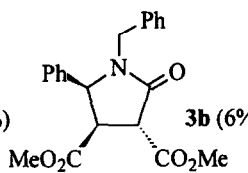
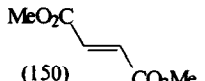
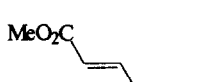
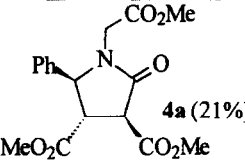
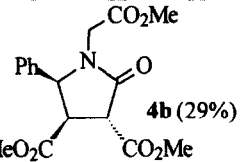
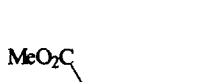
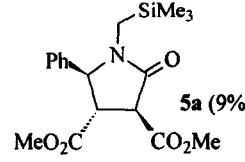
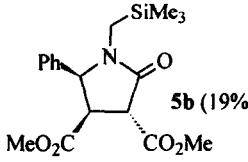
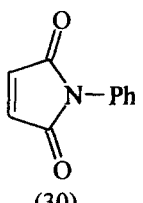
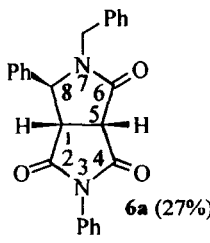
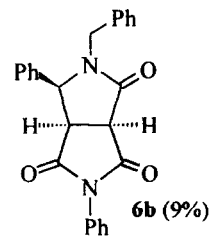
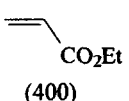
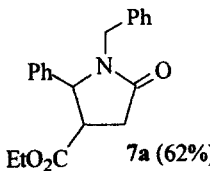
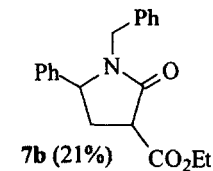
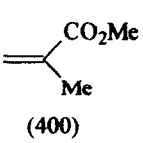
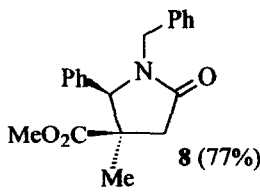
reaction mixture was diluted with Et<sub>2</sub>O (10 ml), filtered, the solvent was removed under a reduced pressure, and the residue was separated by chromatography on silica gel.

All synthesized compounds except pyrrolidinone (**3a**)<sup>7</sup> are new.<sup>12</sup> The configuration of pyrrolidinones (**3b**, **4-6a,b**, **8**) was assessed from the proton chemical shifts of the methoxycarbonyl group at 4-C<sup>13</sup>, the methine protons at 3-C<sup>14</sup> and <sup>1</sup>H-<sup>1</sup>H NOESY data.<sup>15</sup> The *exo* orientation of phenyl in compound (**6a**) and the *endo* orientation of this group in compound (**6b**) was evident from the coupling constants between 1-H and 8-H: <sup>3</sup>J<sub>HH</sub> 1.7 Hz for (**6a**) and <sup>3</sup>J<sub>HH</sub> 10.2 Hz for (**6b**).<sup>16</sup>



GC-MS analysis of the reaction mixtures (Table, runs 1, 2) showed that the primary cycloaddition adducts of the ylide (**1a**) with dimethyl fumarate and maleate represent two pairs of four diastereoisomeric pyrrolidines (**9a, b**). This fact unequivocally confirms the stereospecificity of the cycloaddition step. Lactams from the reaction with dimethyl maleate undergo isomerization at 3-C to give products with a *trans*-CO<sub>2</sub>Me. The tendency of 2-pyrrolidinones with *cis* orientation of the alkoxy carbonyl groups at 3-C and 4-C to stereomutate is well documented.<sup>7</sup> At the same time, the *endo-exo* ratio of the adducts showed no specificity with respect to configuration of the double bond in the dipolarophile: cycloaddition of iminodifluoromethanides (**1a**) to *cis*-olefins (runs 1, 5) furnishes mainly *endo*-adducts, while with *trans*-olefin (runs 2-4) the reaction proceeds with preferable formation of a product with the vicinal substituent *cis* to phenyl. A study of the reaction of *N*-benzylidenebenzylamine with difluorocarbene in the presence of methyl methacrylate and ethyl acrylate showed that cycloaddition of ylide (**1a**) to unsymmetrical dipolarophiles can proceed both regioselectively (run 7) and with formation of two regioisomers (**7a, b**) (run 6). According to NMR spectroscopy data, compounds **7a** and **7b** each are a single stereoisomer, however, the spectral evidence is not suffice to decide between the *cis*- and *trans*-isomers. Thus, in both cases (runs 6, 7) the cycloadditions feature high stereoselectivity.

Table. Reactions of Imines (2a-c) with Difluorocarbene in the Presence of Dipolarophiles.

Run	Imine	R <sup>1</sup>	Dipolarophile (excess, %)	Products (yield)
1	2a	Ph	 (150)	 3a (54%)  3b (6%)
2	2a	Ph	 (150)	3a (13%) 3b (25%)
3	2b	CO <sub>2</sub> Me	 (150)	 4a (21%)  4b (29%)
4	2c	SiMe <sub>3</sub>	 (150)	 5a (9%)  5b (19%)
5	2a	Ph	 (30)	 6a (27%)  6b (9%)
6	2a	Ph	 (400)	 7a (62%)  7b (21%)
7	2a	Ph	 (400)	 8 (77%)

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#### REFERENCES AND NOTES

1. Padwa, A. Ed: 1,3-Dipolar cycloaddition chemistry: Wiley-Interscience: New York, 1984, Vols. I and II.
2. Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Adv Heterocycl. Chem.* **1996**, 65, 93-233.
3. Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Khim. Geterocycl. Soedin.* **1987**, N10, 1336-1342; *Chem. Heterocycl. Comp.* **1987**, N10, 1070-1076.
4. Novikov, M. S.; Khlebnikov, A. F.; Kostikov, R. R. *Zh. Org. Khim.* **1988**, 24, 1917-1922; *J. Org. Chem. USSR* **1988**, 24, 1728-1732.
5. Khlebnikov, A. F.; Novikov, M. S.; Kostikov, R. R. *Zh. Org. Khim.* **1990**, 26, 1899-1903; *J. Org. Chem. USSR* **1990**, 26, 1642-1645.
6. Novikov, M. S.; Khlebnikov, A. F.; Kostikov, R. R. *Zh. Org. Khim.* **1996**, 32, 667-674.
7. Khlebnikov, A. F.; Nikiforova, T. Yu.; Kostikov, R. R. *Zh. Org. Khim.* **1996**, 32, 746-760.
8. Khlebnikov, A. F.; Kostik, E. I.; Kostikov, R. R.; Bepalov, V. Y. *Khim. Geterocycl. Soedin.* **1990**, N3, 355-362; *Chem. Heterocycl. Comp.* **1990**, N3, 304-311.
9. Khlebnikov, A. F.; Kostik, E. I.; Kostikov, R. R. *Synthesis* **1993**, 568-570.
10. Fluorine-containing azomethine ylides have only once been mentioned (McCarthy, J. R.; Barney, C. L.; O'Donnell, J.; Huffman, J. C. *J. Chem. Soc. Chem. Commun.* **1987**, 469-470) as assumed intermediates in formation of ethyl 1-difluoromethyl-3,3-diphenylaziridine-2-carboxylate.
11. Fritz, H. P.; Kornrumpf, W. Z. *Z. Naturforsch.* **1981**, 36b, 1375-1380.
12. All new compounds are fully characterized. The data for selected compounds are: **4a** (oil); IR  $\nu_{\max}$  (CHCl<sub>3</sub>) 1755, 1720 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  7.5-7.2 (m, 5H, ArH), 4.97 (d,  $J=8.1$  Hz, 1H, 5-H), 4.42 and 3.21 (ABq,  $J=17.7$  Hz, 2H, CH<sub>2</sub>), 3.97 (d,  $J=9.7$  Hz, 1H, 3-H), 3.86 (s, 3H, OCH<sub>3</sub>), 3.71 (dd,  $J=9.7, 8.1$  Hz, 1H, 4-H), 3.69 (s, 3H, OCH<sub>3</sub>), 3.67 (s, 3H, OCH<sub>3</sub>); <sup>13</sup>C NMR (62.5 MHz, CDCl<sub>3</sub>)  $\delta$  170.8, 168.9, 168.3, 167.8, 137.4, 129.2, 129.2, 127.9, 127.7, 62.6, 53.2, 52.7, 52.3, 50.8, 49.6, 42.3; MS (70 eV)  $m/z$  (%) 349 (21), 318 (10), 290 (25), 276 (11), 258 (45), 244 (95), 230 (56), 216 (40), 198 (23), 118 (63), 116 (21), 115 (71), 113 (49), 91 (100). **4b** (mp 120-122°C); IR  $\nu_{\max}$  (CHCl<sub>3</sub>) 1755, 1715 cm<sup>-1</sup>; <sup>1</sup>H NMR (250 MHz, CDCl<sub>3</sub>)  $\delta$  7.4-7.0 (m, 5H, ArH), 5.21 (d,  $J=8.6$  Hz, 1H, 5-H), 4.59 and 3.31 (ABq,  $J=17.7$  Hz, 2H, CH<sub>2</sub>), 4.26 (dd,  $J=10.0, 8.6$  Hz, 1H, 4-H), 4.20 (d,  $J=10.0$ , 1H, 3-H), 3.85 (s, 3H, OCH<sub>3</sub>), 3.71 (s, 3H, OCH<sub>3</sub>), 3.31 (s, 3H, 4-CO<sub>2</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (62.5 MHz, CDCl<sub>3</sub>)  $\delta$  169.3, 168.6, 168.4, 168.4, 134.6, 129.2, 128.9, 127.3, 61.6, 53.1, 52.3, 51.9, 48.2, 46.7, 42.5; MS (70 eV)  $m/z$  (%) 349 (15), 318 (6), 290 (22), 276 (10), 258 (39), 244 (100), 230 (38), 216 (38), 198 (25), 118 (72), 116 (17), 115 (62), 113 (47), 91 (89).
13. According to ref. <sup>7</sup> and references cited therein the proton chemical shifts of CO<sub>2</sub>Me *cis* to Ph lie in the range 3.1-3.3 ppm, while *trans* CO<sub>2</sub>Me gives signals at 3.7-3.8 ppm.
14. The deshielding effect of the *cis*-phenyl group shifts the methine protons in compounds (**1b-3b**) low-field (4.20-4.48 ppm) with respect to the corresponding signals in (**1a-3a**) (3.85-3.89 ppm).
15. <sup>1</sup>H-<sup>1</sup>H NOESY experiment with compounds (**1b, 3b**) points to a strong interaction between 4-H and 5-H and a weak interaction between 3-H and 4-H, while in the case of compound (**4b**) there is a strong interaction of 4-H with both 5-H and 3-H.
16. Tsuge, O.; Ueno, K.; Kanemasa, S.; Yorozu, K. *Bull. Chem. Soc. Jpn.* **1986**, 59, 1809-1824.

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