COMMUNICATION

Unprecedented 1,3-dipolar cycloaddition of azomethine ylides to ester carbonyl

Mikhail S. Novikov,[a] Igor V. Voznyi,[a] Alexander F. Khlebnikov,*[a] Jürgen Kopf[b] and Rafael R. Kostikov[a]

[a] *Department of Chemistry, St. Petersburg State University, Universitetskii pr. 26, 198504 St. Petersburg, Petrodvorets, Russia. E-mail: Alexander.Khlebnikov@pobox.spbu.ru; Fax: (+7) 812 4286939*

[b] *Institute of Inorganic Chemistry, Hamburg University, Martin-Luther-King Platz 6, D-20146 Hamburg, Germany*

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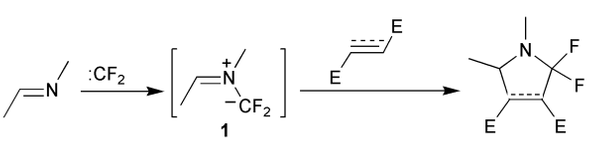
Fluorinated azomethine ylides generated by the reaction of difluorocarbene with aryl and alkyl imines of *O*-acylated salicylaldehyde undergo intramolecular 1,3-dipolar cycloaddition across the ester carbonyl to give 2,8-dioxa-6-azabicyclo[3.2.1]octane derivatives.

Cascade carbene–ylide reaction sequences which allow three and more new bonds to be formed in one synthetic operation are useful tools for preparing nitrogen-containing heterocycles. Among them the carbene (or metallo carbenoid) formation–ylide formation–1,3-dipolar cycloaddition methodology is one of the most effective and synthetically versatile.[1] The range of multiple bonds that display dipolarophilic activity toward azomethine ylides in intermolecular reactions include carbon–carbon double and triple bonds activated by electron-withdrawing groups,[2] and, to a lesser extent, the carbon–nitrogen double bond of imines[3] and the carbon–oxygen double bond of aldehydes.[4] Intramolecular cycloadditions can also be performed with nonactivated carbon–carbon double[5] and triple[6] bonds, as well as furan[7] and, in extremely harsh conditions, benzene[8] double bonds.

Iminiodifluoromethanides **1** readily cycloadd to alkenes[9] and alkynes[10] in either the intermolecular or intramolecular[11] fashion (Scheme 1). Examples of intermolecular cyclo-



Scheme 1

addition of iminiodifluoromethanides to the carbonyl function of acetaldehyde, benzaldehyde, and acetone[12] are also known.

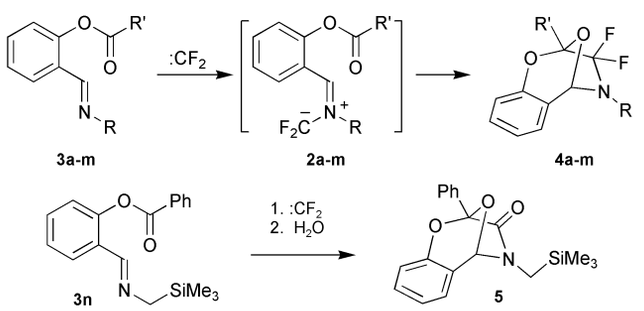
In this communication we present the first example of 1,3-dipolar cycloaddition of azomethine ylides to ester carbonyl.

Ester carbonyls are considered to be inactive toward azomethine ylides. For this reason, the alkoxycarbonyl function is widely used for activation of C=C and C≡C bonds in cycloadditions. The electronic factor responsible for reduced activity of an ester C=O double bond compared with an aldehyde C=O double bond in 1,3-dipolar cycloaddition reactions is the relatively high LUMO energy of the former. We supposed that the extremely favorable entropy factor which often offsets unfavorable electronic factors in intramolecular cycloadditions would allow successful cycloaddition of azomethine ylides to an ester C=O double bond.

Actually, it was found that reaction of ylide **2a**, generated from imine **3a** and difluorocarbene,[10b] gives rise to an adduct across the ester C=O double bond, a bridged compound **4a**, in 74% yield. This result proved to be quite general for the series of *N*-aryl substituted imines **3a**–**l** (Table 1), as well as some *N*-alkyl imines, *e.g.* compounds **3m**, **n** (Scheme 2).[13]

Table 1 Preparation of compounds **4a**–**m**

	R	R′	Time/h	Yield (%)
4a	Ph	Ph	72	74
4b	Ph	4-$MeOC_6H_4$	19	92
4c	Ph	4-NCC_6H_4	4	70
4d	Ph	2,4-$Cl_2C_6H_3$	80	73
4e	Ph	1-Naphthyl	95	75
4f	Ph	CH_2=CMe	17	77
4g	Ph	(*E*)-MeCH=CH	110	68
4h	Ph	(*E*)-PhCH=CH	20	56
4i	Ph	(*E*)-PhCH=CPh	80	70
4j	4-BrC_6H_4	2-Furyl	37	75
4k	4-BrC_6H_4	Ph	56	85
4l	2,4-$Cl_2C_6H_3$	Ph	85	70
4m	$(4\text{-}ClC_6H_4)_2CH$	Ph	17	88



Scheme 2

The compounds **4a**–**m** † [14] are fairly stable and are best stored in the crystalline state at +4 °C. The primary cycloadduct of the ylide generated from imine **3n** undergoes rapid hydrolysis under chromatographic purification conditions to lactam **5** which was isolated in 67% yield.[14] Note compounds **4a**–**m** are hydrolyzed in the same way on exposure on silica for a long time, whereas in chloroform solutions at room temperature they undergo cleavage by the bicyclic skeleton. For example, after keeping compound **4k** in a chloroform solution for 3.5 months, salicylaldehyde and *N*-(4-bromophenyl)phenylglyoxylamide (62%) were isolated.

Thus, intramolecular cycloaddition of ylides **2a**–**n** across ester C=O bond proceeds with complete regioselectivity to give 2,8-dioxa-6-azabicyclo[3.2.1]octane bridged compounds. The observed regioselectivity agrees with that characteristic of intermolecular cycloaddition of fluorinated azomethine ylides to the C=O bond of aldehydes and ketones,[12] where the ylide difluoromethylene fragment adds to the carbonyl carbon.

Attempted extension of the above reaction to difluoro ylide **7** which involves a 4-atomic tether between ester C=O and dipole moieties failed: no intramolecular cycloaddition products **8** and **9** could be detected.

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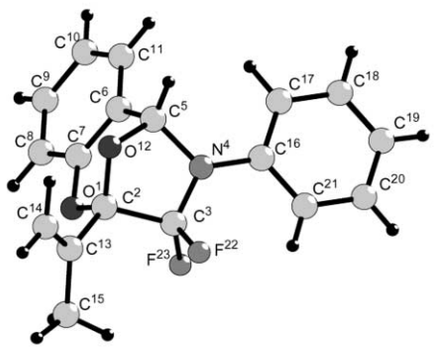
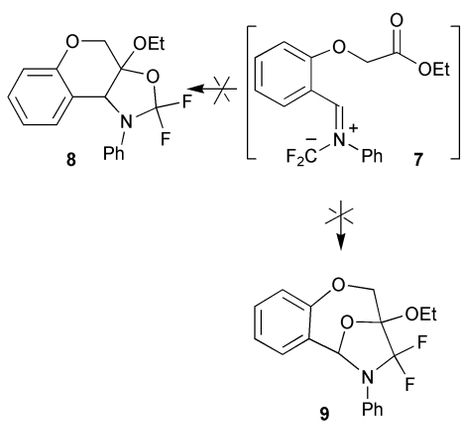


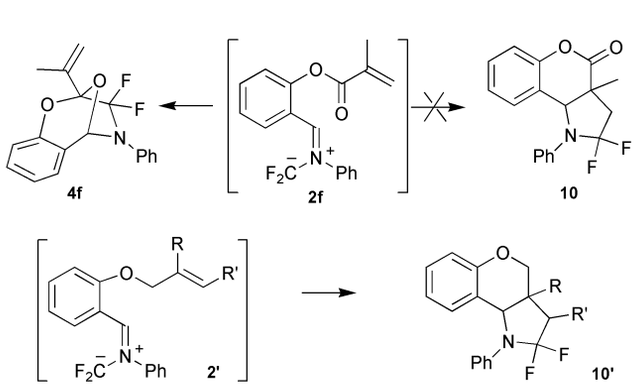
Fig. 1 X-Ray crystal structure of compound **4f**.

A probable explanation for this result is that to form fused compound **8** requires the unfavorable approach of the ylide to the C=O bond (the difluoromethylene fragment of the ylide should add to the carbonyl carbon), whereas at the opposite orientation of the ylide and dipolarophile, a seven-membered ring incorporated in bicyclo[4.2.1]nonane bridged system **9** (Scheme 3) should be formed, which is unfavored kinetically.



Scheme 3

An unexpected result was the failure of intramolecular cycloaddition of ylide **2f** across the activated C=C bond to form fused system **10**; instead, C=O double bond adduct **4f** formed (Scheme 4). At the same time, examples of facile formation of



Scheme 4

systems **10′** by cycloaddition of fluorinated azomethine ylides **2′** across both activated and nonactivated multiple carbon–carbon bonds have been reported.[11] Intermediates **2f** and **2′** differ in that the 4-atomic tether between the dipole and dipolarophile fragments in the former has one more sp^2 center. Hence, the lack of products like **10** is probably explained by an excessively high rigidity of the 4-atomic tether with three sp^2 centers, preventing effective overlap of orbitals of the dipole and C=C bond. Reasons for the observed reactivity of ylide **2f** are now under *ab initio* computations.

Acknowledgements

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Notes and references

† All new compounds have been fully characterised using standard spectroscopic and analytical methods. The structure of cycloadduct **4f**, was established by single-crystal X-ray diffraction (Fig. 1). Crystal data. $C_{18}H_{15}F_2NO_2$, M = 315.32, monoclinic, a = 12.0236(5), b = 6.5832(4), c = 18.8618(8) Å, β = 99.72(0), U = 1471.55(13) Å^3, T = 153 K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo-Kα) = 0.11 mm^{-1}, 14655 reflections measured, 3343 unique (R_{int} = 0.0673) which were used in all calculations. The final value of R was 0.045 (all data). CCDC reference number 185601. See http://www.rsc.org/suppdata/p1/b2/b204464a/ for crystallographic files in .cif or other electronic format.

1 (*a*) A. Padwa and M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223; (*b*) A. F. Khlebnikov, M. S. Novikov and R. R. Kostikov, *Adv. Heterocycl. Chem.*, 1996, **65**, 93.

2 *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, John Wiley & Sons, New York, 1984, vol. 1,2.

3 (*a*) Z. Bende, K. Simon, G. Tóth, L. Töke and L. Weber, *Liebigs Ann. Chem.*, 1982, 924; (*b*) Z. Bende, I. Bitter, L. Töke, L. Weber, G. Tóth and F. Janke, *Liebigs Ann. Chem.*, 1982, 2146; (*c*) A. Szöllösy, T. Tischer, I. Kádas, L. Töke and G. Tóth, *Tetrahedron*, 1999, **55**, 7279.

4 O. Tsuge and S. Kanemasa, *Adv. Heterocycl. Chem.*, 1989, **45**, 231.

5 For some recent examples, see (*a*) J. D. Harling and B. S. Orlek, *Tetrahedron*, 1998, **54**, 14905; (*b*) O. Irie, K. Samizu, J. R. Henry and S. M. Weinreb, *J. Org. Chem.*, 1999, **64**, 587; (*c*) B. B. Snider, Y. Ahn and B. M. Foxman, *Tetrahedron Lett.*, 1999, **40**, 3339; (*d*) Q. Cheng, W. Zhang, Y. Tagami and T. Oritani, *J. Chem. Soc., Perkin Trans. 1*, 2001, 452; (*e*) I. Coldham, K. M. Crapnell, J. D. Moseley and R. Rabot, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1758; (*f*) H. Mahmud, C. J. Lovely and H. V. R. Dias, *Tetrahedron*, 2001, **57**, 4095.

6 (*a*) O. Tsuge and K. Ueno, *Heterocycles*, 1983, **20**, 2133; (*b*) P. DeShong, D. A. Kell and D. R. Sidler, *J. Org. Chem.*, 1985, **50**, 2309; (*c*) M. Westling, R. Smith and T. Livinghouse, *J. Org. Chem.*, 1986, **51**, 1159; (*d*) L. M. Harwood and L. C. Kitchen, *Tetrahedron Lett.*, 1993, **34**, 6603; (*e*) E. Vedejs, A. Klapars, B. N. Naidu, D. W. Piotrowski and F. C. Tucci, *J. Am. Chem. Soc.*, 2000, **122**, 5401.

7 O Tsuge, K. Ueno and S. Kanemasa, *Chem. Lett.*, 1984, 797.

8 B. R. Henke, A. J. Kouklis and C. H. Heathcock, *J. Org. Chem.*, 1992, **57**, 7056.

9 (*a*) M. S. Novikov, A. F. Khlebnikov, A. E. Masalev and R. R. Kostikov, *Tetrahedron Lett.*, 1997, **38**, 4187; (*b*) A. F. Khlebnikov, M. S. Novikov and R. R. Kostikov, *Mendeleev Commun.*, 1997, 145.

10 (*a*) M. S. Novikov, A. F. Khlebnikov, E. S. Sidorina and R. R. Kostikov, *J. Fluorine Chem.*, 1998, **90**, 117; (*b*) M. S. Novikov, A. F. Khlebnikov, E. S. Sidorina and R. R. Kostikov, *J. Chem. Soc., Perkin Trans. 1*, 2000, 231.

11 M. S. Novikov, A. F. Khlebnikov, O. V. Besedina and R. R. Kostikov, *Tetrahedron Lett.*, 2001, **42**, 533.

12 M. S. Novikov, A. F. Khlebnikov, A. Krebs and R. R. Kostikov, *Eur. J. Org. Chem.*, 1998, 133.

13 A typical procedure of preparation of compounds **4**, **5** was as follows. A flask containing active lead[10b] (1.2 g, 5.8 mmol) and CH_2Cl_2 (7 cm^3) was charged with Bu_4NBr (2.0 g, 6.0 mmol), imine (2.7 mmol), and CBr_2F_2 (1.95 g, 9.3 mmol). The flask was tightly stoppered, and the mixture was irradiated with ultrasound at 45 °C until the lead was consumed completely. Chromatography (hexane–ethyl acetate, 4 : 1) followed by recrystallization provided compounds **4**, **5**.

14 Data for **4a**: mp 138–140 °C (hexane–AcOEt); MS (70 eV), *m*/*z* (%): 352 (8), 351 (M^+, 39), 246 (8), 196 (5), 181 (28), 152 (3), 127 (6), 106 (6), 105 (100), 77 (24); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.38 (d, 1H, $^4J_{HF}$ 6.2 Hz, H^5), 6.96–7.91 (m, 14H, H^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 86.2 (C^5), 104.3 (dd, J_{CF} 26.0, 33.7 Hz, C^2), 115.1, 116.2, 120.6 (C^{Ar}), 121.3 (dd, J_{CF} 258, 262 Hz, C^3), 121.6, 122.1 (d, J_{CF} 5.0 Hz), 124.0, 125.9, 128.0, 129.1, 129.9, 130.4, 131.9, 136.4 (dd, J_{CF} 1.5, 3.4 Hz), 150.5 (C^{Ar}); ^{19}F NMR ($CDCl_3$, C_6F_6): δ 57.52 (d, J_{FF} 176 Hz), 88.79 (d J_{FF} 176 Hz); calc. for $C_{21}H_{15}F_2NO_2$: C 71.79; H 4.30; N 3.99; found C 71.79; H 4.31; N 3.77%. (**4f**): mp 104–106 °C (hexane); MS (70 eV), *m*/*z* (%): 316 (13), 315 (M^+, 60), 246 (21), 196 (10), 181 (100), 180 (3), 152 (6), 131 (3), 104 (5), 77 (14), 69 (20); ^{1}H

NMR (300 MHz, $CDCl_3$): δ 2.12 (s, 3H, Me), 5.40 (s, 1H, CH_2), 5.71 (s, 1H, CH_2), 6.25 (d, 1H, $^4J_{HF}$ 6.2 Hz, H^5), 6.92–7.37 (m, 9H, H^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.1 (d, J_{CF} 1.7 Hz, CH_3), 86.0 (C^5), 104.4 (dd, J_{CF} 25.4, 34.8 Hz, C^2), 115.2 (t, J_{CF} 2.5 Hz), 116.1 (C^{Ar}), 116.4 (=CH_2), 120.4 (C^{Ar}), 121.4 (dd, J_{CF} 258, 263 Hz, C^3), 121.6, 122.1 (d, J_{CF} 5.0 Hz), 124.0, 129.1, 130.3, 135.9 (C^{Ar}), 136.3 (dd, *C*Me, J_{CF} 2.2, 3.9 Hz), 150.5 (C^{Ar}); ^{19}F NMR ($CDCl_3$, C_6F_6): δ 59.81 (d, J_{FF} 176 Hz), 84.50 (d, J_{FF} 176 Hz); calc. for $C_{18}H_{15}F_2NO_2$: C 68.57; H 4.79; N 4.44; found C 68.45; H 4.90; N 4.42%. **5**: mp 104–105 °C (hexane–Et_2O); IR (CCl_4, cm^{-1}): ν 1745; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 9H, CH_3), 2.34 (d, 1H, *J* 15.3 Hz, CH_2), 3.01 (d, 1H, *J* 15.3 Hz, CH_2), 5.71 (s, 1H, H^5), 6.96–7.87 (m, 9H, H^{Ar}); ^{13}C NMR (75 MHz, $CDCl_3$): δ −2.0 (CH_3), 30.5 (CH_2), 87.2 (C^5), 100.2 (C^2), 117.2, 120.2, 121.4, 123.9, 126.1, 128.0, 129.6, 130.5, 132.8, 151.4 (C^{Ar}), 165.7 (C=O); calc. for $C_{19}H_{21}NO_3Si$: C 67.23; H 6.24; N 4.13; found C 66.85; H 6.19; N 4.46%.