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High Diastereoselectivity in Intermolecular Carbonyl Ylide Cycloaddition with Aryl Aldehyde Using Methyl Diazo(trifluoromethyl)acetate

Biao Jiang,* Xiaobing Zhang, and Zhaohui Luo

The State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic
Chemistry, Chinese Academy of Sciences, 354 Fenglin Road,
Shanghai 200032, P. R. China

jiangb@pub.sioc.ac.cn

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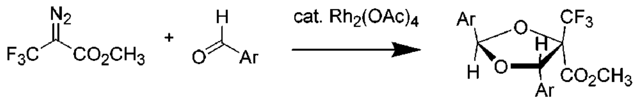
ABSTRACT



Methyl diazo(trifluoromethyl)acetate undergoes $Rh_2(OAc)_4$ catalyzed reaction with aryl aldehyde to form 1,3-dioxolanes bearing a C-4 trifluoromethyl group diastereoselectively in excellent yield.

Catalytic methods for the generation of metallocarbenes have received a great deal of attention in recent years. The metal-catalyzed reaction of α-diazo-carbonyl compounds is not limited to cyclopropanation, even though the focus of many studies has centered on this transformation.[1] Metallocarbenoid reactions involving either X−H insertions or ylide generation have also been used to prepare complex synthetic targets.[2] The catalytic generation of carbonyl ylides from diazo compounds, especially in the intramolecular reaction, have significantly broadened their applicability for natural product syntheses.[3] Intermolecular reactions emanating from transition metal catalyzed diazo decomposition in the presence of aldehydes or ketones have received limited attention. Early investigation by Huisgen and de March with symmetric dimethyl diazomalonate revealed that a mixture of two major dioxolane stereoisomers was formed in the $Cu(acac)_2$, $Rh_2(OAc)_4$, or $Cu(OTf)_2$ catalyzed reactions with benzaldehyde.[4] Recently, Doyle reported several cases where ethyl diazoacetate undergoes dirhodium(II)-catalyzed reaction with aryl aldehyde to form 1,3-dioxolane as a mixture of diastereoisomers in good yields.[5]

Our interest in this field is focused on the synthesis of diazo compounds bearing a trifluoromethyl group and their use in the synthesis of specifically trifluoromethylated molecules through transition metal catalyzed decomposition, which is an ongoing area of research due to the unique physical and biological properties imparted by the CF_3 group.[6] In our studies, advantage has been taken of the trifluoromethyl group that can act as an electron withdrawing group necessary for the stabilization of the diazo group and avoids the problem of 1,2-hydrogen shift commonly encountered in cases where the carbene carbon is substituted by a simple alkyl group.[7]

In an earlier study, we have identified rhodium acetate as the catalyst that smoothly decomposes methyl diazo(trifluoromethyl)acetate (**1**) at room temperature. Thus, methyl diazo-

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[1] (a) Padwa, A.; Austion, D. J. *Angew. Chem., Int. Engl.* **1994**, *33*, 1797. (b) Padwa. A. *Acc. Chem. Res.* **1991**, *24*, 22.

[2] Padwa, A.; Hornbuckle, S. *Chem. Rev.* **1991**, *91*, 263.

[3] Taber, D. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, p 1045.

[4] (a) de March, P.; Huisgen, R. *J. Am. Chem. Soc.* **1982**, *104*, 4952. (b) Huisgen, R.; de March, P. *J. Am. Chem. Soc.* **1982**, *104*, 4953.

[5] (a) Doyle, M. P.; Forbes, D. C.; Protopopova, M. N.; Stanley, S. A.; Vasbinder, M. M.; Xavier, K. R. *J. Org. Chem.* **1997**, *62*, 7210. (b) Doyle, M. P.; Forbes F. C.; Xavier, K. R. *Russ. Chem. Bull.* **1998**, *47*, 932

[6] (a) Shi, G. Q.; Xu, Y. Y. *Chem. Commun.* **1989**, 607. (b) Shi, G. Q.; Xu, Y. Y. *J. Org. Chem.* **1990**, *55*, 3383. (c) Shi, G. Q.; Xu, Y. Y.; Xu**,** M. *Tetrahedron* **1991**, *47*, 1629. (d) Shi, G. Q.; Cao, Z. Y.; Cai, W. L. *Tetrahedron* **1995**, *51*, 5011.

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(trifluoromethyl)acetate was treated with 2 equiv of aryl aldehyde **2** in CH_2Cl_2 with rhodium(II) acetate as a catalyst. The reaction was finished in a few hours to give carbonyl ylide cycloaddition products in high yields[8] (Scheme 1). To our surprise, the reaction of aryl aldehydes bearing a substituted group in the *meta* or *para* position diastereoselectively gave a single cycloaddition isomer identified as **4** out of the four possible diastereomers (Table 1, entries 1−5). This was different from the case of diazoacetate, in which the two isomers were produced with a 1:1 ratio and in less than 15% yield.[4] The *ortho*-substituted aryl aldehydes also afforded **4** as the major product in a ratio of 9:1 (Table 1, entries 6−7).

Scheme 1

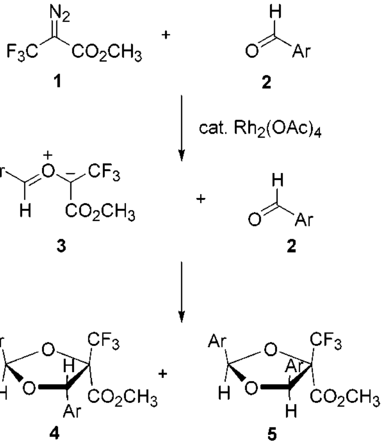

Table 1. Reaction of Methyl Diazo(trifluoromethyl)acetate and Aryl Aldehyde Catalyzed by $Rh_2(OAc)_4$

entry	Ar in **2**	product	isomer ratio[a]	yield (%)[b]
1	p-ClC_6H_4 (**2a**)	**4a**	100:0	82
2	p-FC_6H_4 (**2b**)	**4b**	100:0	89
3	p-$MeOC_6H_4$ (**2c**)	**4c**	100:0	95
4	m-$PhOC_6H_4$ (**2d**)	**4d**	100:0	94
5	m-$MeOC_6H_4$ (**2e**)	**4e**	100:0	85
6	o-$CHOC_6H_4$ (**2f**)	**4f** + **5f**	90:10	82
7	o-ClC_6H_4 (**2g**)	**4g** + **5g**	91:9	91

[a] Determined by ^{19}F NMR. [b] Isolated yield.

Table 2. ^1H NMR and ^{19}F NMR Chemicals for **4** and **5**

compd	H2	H5	CH_3	$^{19}F(CF_3)$
4a	6.71	5.56	3.39	−3.6
4b	6.74	5.60	3.38	−3.4
4c	6.71	6.20	3.36	−3.6
4d	6.67	5.55	3.40	−3.5
4e	6.71	5.60	3.37	−4.0
4f	7.61	6.93	3.39	−4.3
5f	7.21	6.60	4.08	−6.0
4g	7.13	6.14	3.44	−5.0
5g	6.71	6.03	3.97	−5.8

The stereochemistry of the carbonyl ylide cycloaddition products could not be firmly established from the NMR data. However, compounds **4f** and **5f** were separated by silica gel chromatography, allowing us to firmly establish the stereochemistries of both compounds and therefore confirm the stereochemistry inferred for the other compounds. The X-ray structure analysis of **4f** gave clear evidence of the *trans* relationship between the two aryl rings and a *cis* relationship between the C-4 CO_2Me and the C-5 aryl ring (Figure 1). The NOESY spectrum of **5f** showed a correlation for H-2 to H-5, indicating a *cis* relationship between the two aryl rings. On the basis of the ^{19}F NMR spectrum, the CF_3 group (δ −4.3 ppm) in **4f** is considerably deshielded with respect to the CF_3 group (δ −6.0 ppm) in **5f**, indicating that the two aryl ring and C-5 CF_3 in **5f** were all in a *cis* relationship. Doyle has made a similar observation in the reaction of diazoacetate with aryl aldehyde.[4] Finally by comparing the NMR data of **4** with **4f**, the configuration of **4** is tentatively assigned as (2R*,4S*,5S*).

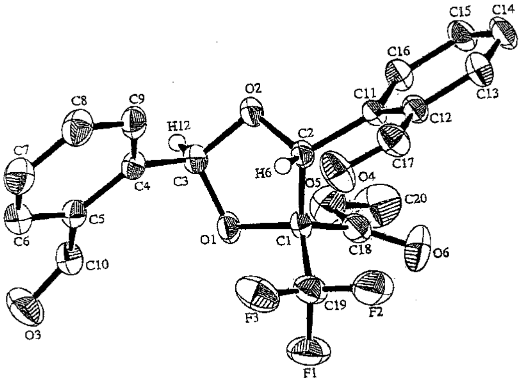

Figure 1. X-ray crystallography of **4f**.

To study the mechanism of the carbonyl ylide cycloaddition, the head of formation (HOF) of the four possible conformations of the carbonyl ylide was calculated in the semiemperical level by using AM1 homitonians (Figure 2). Other conformations of carbonyl ylide were impossible for the planar form, otherwise their energies were much higher than these planar ones. Notably, the energy of the carbonyl

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(7) For example: (a) Taber, D. F.; Hoerrner, R. S. *J. Org. Chem.* **1992**, *57*, 441. (b) Taber, D. F.; Hennessy, M. J.; Louey, J. P. *J. Org. Chem.* **1992**, *57*, 436.

(8) General procedure for preparation of 1,3-dioxolane: To a solution of aryl aldehyde (4.5 mmoL) and rhodium acetate (10 mg) in CH_2Cl_2 (5 mL) was added methyl diazo(trifluoromethyl)acetate (2 mmoL) in CH_2Cl_2 (5 mL) at the rate of 1.0 mL/h under a nitrogen atmosphere at room temperature. After the addition was completed, the reaction mixture was stirred for an additional 2 h. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel eluted with petroleum ether (60−90 °C) and ethyl acetate (15:1) to afford 1,3-dioxolane.

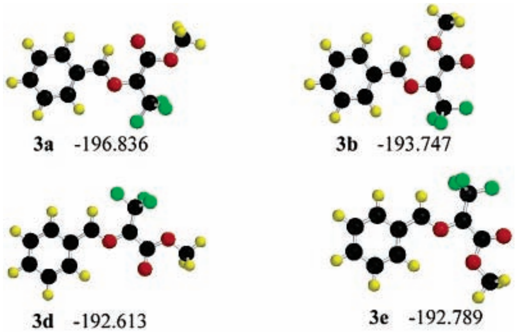

Figure 2. Heat of formation (HOF, in kal/mol) of **3**.

ylide (**3a**) was lowest. Therefore, the highly diastereoselective carbonyl ylide addition could be accounted for by invoking the involvement of a low-energy planar geometric carbonyl ylide (**3a**) (Scheme 1).[4,9]

In summary, we report that the Rh(II)-catalyzed reaction between methyl diazo(trifluoromethyl)acetate with aryl aldehyde afforded the 1,3-dioxolane bearing a C-4 trifluoromethyl group with remarkable diastereoselectivity and in excellent yield. The presence of a trifluoromethyl group in C-4 should be useful for further synthetic transformation of the heterocycles.

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Supporting Information Available: NMR data for all compounds prepared and details of the X-ray diffraction data of compound **4f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Alt, M.; Mass, G. *Tetrahedron* **1994**, *50*, 7435.