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Stereoselective Iodine Atom Transfer [3 + 2] Cycloaddition Reaction with Alkenes Using Unsymmetrical Allylated Active Methine Radicals

Osamu Kitagawa, Shinsaku Miyaji, Chiseko Sakuma, and Takeo Taguchi*

Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

taguchi@ps.toyaku.ac.jp

Received December 4, 2003

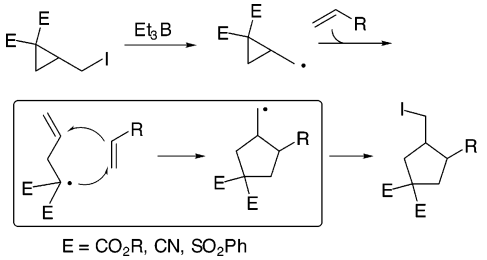
Abstract: Treatment of 1-diethylphosphonyl- or 1-phenylsulfonyl-2-(iodomethyl)cyclopropane-1-carboxylate with Et_3B leads to an unsymmetrical allylated active methine radical species that gives functionalized cyclopentane derivatives with high stereoselectivity through iodine atom transfer [3 + 2] cycloaddition reaction with alkenes.

Allylated active methine radicals (electrophilic homoallyl radicals) provide a powerful means for synthesis of cyclopentane derivatives through [3 + 2] cycloaddition reaction with simple alkenes (lacking any activating groups).[1] Recently, we reported radical iodine atom transfer [3 + 2] cycloaddition using dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate (E = CO_2Me) and 1,1-bisphenylsulfonyl-2-(iodomethyl)cyclopropane (E = $PhSO_2$) as novel allylated active methine radical precursors (Scheme 1).[2] In comparison with the reactions of other groups, our method using these iodomethylcyclopropane derivatives can be widely applied to reaction with various alkenes such as 1-alkene, 1,1-disubstituted alkene, 1,2-disubstituted alkene, 1,4-diene, and enol ether.[2] Furthermore, a higher level of relative stereocontrol is also observed, because our reaction can be performed at lower temperature.

On the other hand, in contrast with the reaction of symmetrical radical species such as allylated malonate radical, the reaction with an unsymmetrical allylated active methine radical possessing two different electron-withdrawing groups has so far been uncommon. Although a few examples using an unsymmetrical allylated active methine radical have been reported, the generality and stereochemical detail have not been described.[1b,d] This may be due to the lack of a suitable radical precursor and diastereomeric complication of the product caused by the low stereoselectivity of the reaction. We expected that our methodology using an iodoalkylated three-membered ring compound as a radical precursor would be applicable to the generation of an unsymmetrical allylated active methine radical and its reaction with alkenes.[3] In this paper, we report an iodine atom transfer [3 + 2] cycloaddition reaction with alkenes using 1-diethylphosphonyl- or 1-phenylsulfonyl-2-(iodomethyl)cyclopropane-1-carboxylate as novel unsymmetrical allylated active methine radical precursors. The present reaction proceeds with high diastereoselectivity to give functionalized cyclopentane derivatives having two or three chiral carbons.

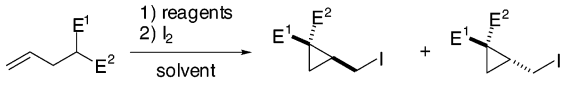
Iodomethylcyclopropane derivatives **1** and **2** having an ester group and a diethylphosphonyl or phenylsulfonyl group were chosen as radical precursors, because they can be easily prepared through iodocarbocyclization of allylated active methine compounds, which was previously found by us and Beckwith's group (Scheme 2).[4,5] Moreover, substituted cyclopentane products having a phosphonyl group, may be also regarded as conformationally restricted analogues of phosphonic acid derivatives possessing useful biological properties.[6] In the

SCHEME 1



E = CO_2R, CN, SO_2Ph

SCHEME 2



[E^1=CO_2Et, E^2=P(O)$(OEt)_2$]		**1** (*trans*)	**1'** (*cis*)
[E^1=CO_2Me, E^2=SO_2Ph]		**2** (*trans*)	**2'** (*cis*)
reagent	solvent	**1** or **2** (yield)	ratio of **1**/**1'** or **2**/**2'**
$TiCl_4$-Et_3N	CH_2Cl_2	**1** (78 %)	**1**/**1'**=2
NaH	THF	**2** (60 %)	**2**/**2'**=14

* Corresponding author: Phone and Fax: +81-426-76-3257.

(1) (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (b) Miura, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5135. (c) Curran, D. P.; Chen, M.; Spletzer, E.; Seong, C. M.; Chang, C. *J. Am. Chem. Soc.* **1989**, *111*, 8872. (d) Snider, B. B.; Buckman, B. O. *Tetrahedron* **1989**, *45*, 6969. (e) Singleton, D. A.; Church, K. M. *J. Org. Chem.* **1990**, *55*, 4780. (f) Chuang, C. P.; Hou, S. S.; Ngoi, T. H. J. *J. Chem. Res., Synop.* **1991**, 216−217. (g) Maslak, V.; Cekovic, Z.; Saicic, R. N. *Synlett* **1998**, 1435. Examples of stepwise radical [3 + 2] cycloaddition: (h) Curran, D. P.; Seong, C. *Tetrahedron* **1992**, *48*, 2157. (i) Curran, D. P.; Seong, C. *Tetrahedron* **1992**, *48*, 2175. For reviews: (j) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091. (k) McCarroll, A, J.; Walton, J. C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3215. (l) Rheault, T. R.; Sibi, M. P. *Synthesis* **2003**, 803.

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(5) Beckwith, A. L.; Zozer, M. J. *Tetrahedron Lett.* **1992**, *33*, 4975.

(6) Fairlamb, I. J. S.; Pike, A. C.; Ribrioux, S. P. C. P. *Tetrahedron Lett.* **2002**, *43*, 5327.

10.1021/jo035771a CCC: $27.50 © 2004 American Chemical Society
Published on Web 03/02/2004

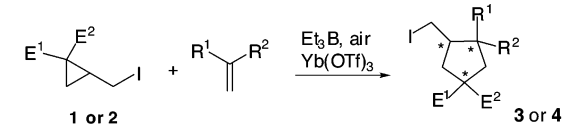
iodocarbocyclization of allylated phosphonoacetate and sulfonyl acetate, *trans*-iodomethylcyclopropanes **1** and **2** were obtained as a major diastereomer.[7] The stereochemistries of **1** and **2** were determined by ^{13}C NMR analysis.[8] Treatment of **1** and **2** with Et_3B would produce an unsymmetrical allylated active methine radical through regioselective C−C bond cleavage of the resulting cyclopropylmethyl radical, which would in turn react with alkenes through the iodine atom transfer mechanism to give iodoalkylated cyclopentane derivatives.[1j,9]

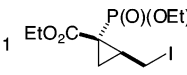
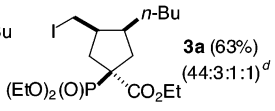
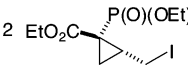
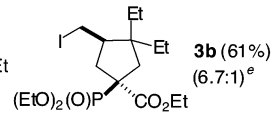
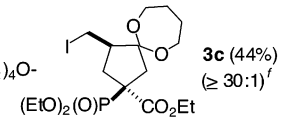
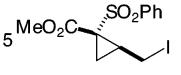
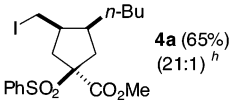
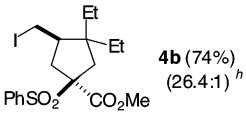
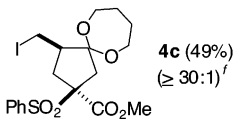
The radical iodine atom transfer [3 + 2] cycloaddition of **1** and **2** with alkenes was examined (Table 1). When the reaction of **1** with 1-hexene (2 equiv) was performed under our previously determined conditions [Et_3B[10] and $Yb(OTf)_3$ in CH_2Cl_2],[2] cycloaddition product **3a** was obtained in 63% yield as a diastereomeric mixture (entry 1). In this reaction, four possible diastereomers were produced with relatively high stereoselectivity (diastereomer ratio = 44:3:1:1). The addition of $Yb(OTf)_3$ is required to obtain the product **3a** in a good yield; that is, in the absence of $Yb(OTf)_3$, **3a** was obtained in lower chemical yield (48%) but with similar diastereoselectivity. As described in the previous paper, $Yb(OTf)_3$ may enhance the reactivity of the phosphonoacetate radical through the formation of a more electrophilic radical by the bidentate coordination by the ester and phosphonyl groups.[11]

A similar diastereoselectivity and a chemical yield were also observed in the reaction with *cis*-iodomethylcyclopropane **1′** (66%, diastereomer ratio = 42:3:1:1, entry 2). This result indicates that in the present reaction, a diastereomeric mixture of **1** and **1′** can be used as a radical precursor without separation. The reaction with 1,1-disubstituted alkene such as 2-ethyl-1-butene also proceeds under the same conditions to give the product **3b** in 61% yield and in a diastereomeric ratio of 6.7:1 (entry 3).[12] In the reaction with ketene acetal, further increase in the stereoselectivity was observed; the product **3c** was obtained with almost complete diastereoselectivity (≥30:1) but in moderate yield (44%, entry 4). In this case, since the addition of $Yb(OTf)_3$ resulted in the decomposition of ketene acetal, the reaction was performed in the presence of only Et_3B.

Similar to phosphonyl derivative **1**, the reaction of methyl 1-phenylsulfonyl-2-(iodomethyl)cyclopropane-1-carboxylate **2** also proceeds smoothly to give the products **4** in good yields. In the reaction of sulfonyl derivative **2**, better diastereoselectivity than that with phosphonyl derivative **1** was observed. For example, in the reaction of **2** with 1-hexene, among possible four diastereomers, only two diastereomers were obtained in a high ratio (21:1, 65% yield) (entry 5). The reaction with 2-ethyl-1-butene also proceeded in a highly diastereoselective manner (diastereomer ratio = 26:1) to give the product **4b** in 74% yield (entry 6). In the reaction with ketene acetal, almost

TABLE 1. Iodine Atom Transfer [3 + 2] Cycloaddition Reaction of 1 or 2 with Alkenes[a]



entry	**1** or **2**	alkene	**3** or **4**[b] (yield[c], diastereomer ratio)
1	 **1**	R^1=*n*-Bu, R^2=H	 **3a** (63%) (44:3:1:1)[d]
2	 **1′**	R^1=*n*-Bu, R^2=H	**3a** (66%) (42:3:1:1)[d]
3	**1**	$R^1=R^2$=Et	 **3b** (61%) (6.7:1)[e]
4[g]	**1**	$R^1=R^2$= -O(CH_2)$_4$O-	 **3c** (44%) (≥ 30:1)[f]
5	 **2**	R^1=*n*-Bu, R^2=H	 **4a** (65%) (21:1)[h]
6	**2**	$R^1=R^2$=Et	 **4b** (74%) (26.4:1)[h]
7[g]	**2**	$R^1=R^2$= -O(CH_2)$_4$O-	 **4c** (49%) (≥ 30:1)[f]

[a] Radical reaction: **1** or **2** (0.5 mmol), alkenes (1 mmol), Et_3B (0.5 mmol), $Yb(OTf)_3$ (0.5 mmol) in CH_2Cl_2 (4 mL) at −15−0 °C. [b] Structure of the major stereoisomer is shown. [c] Isolated yield. [d] Ratio was determined on the basis of the combination of 300 MHz ^1H NMR and the isolated yield. [e] Ratio based on the isolated yield. [f] Minor diastereomer was not detected by 300 MHz ^1H NMR. [g] Reaction was carried out without the addition of $Yb(OTf)_3$. [h] Ratio based on 300 MHz ^1H NMR.

(7) Although the iodocyclopropanation reaction of allylphosphonoacetate was also examined under Beckwith's conditions (NaH, I_2), the desired products **1** and **1′** were not obtained. In the case of reaction with allylphenylsulfonyl acetate, the products **2** and **2′** were also obtained in similar chemical yield by using our method ($TiCl_4$−Et_3N, I_2). However, in comparison with Beckwith's method, a remarkable decrease in the diastereoselectivity was observed (**2**/**2′** = 1.5).

(8) Stereochemistries of **1** and **2** were determined on the basis of the chemical shift of the ester carbonyl carbon in ^{13}C NMR. That is, carbonyl carbons of major products **1** and **2** should appear upfield from those of minor products **1′** and **2′**, because of the influence of the iodomethyl group at the cis position. Moreover, the stereochemical assignments of **1** and **1′** were also supported by J_{C-P} values. In major isomer **1**, C−P coupling (J_{C-P} = 4.0 Hz) between the iodomethyl carbon and the P atom was observed, while no C−P coupling in **1′** was detected. Minami, T.; Yamanouchi, T.; Tokumasu, S.; Hirai, I. *Bull Chem. Soc. Jpn.* **1984**, *57*, 2127.

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(12) Reaction in the absence of $Yb(OTf)_3$ resulted in remarkable decrease in the chemical yield of the product **3b** (26%).

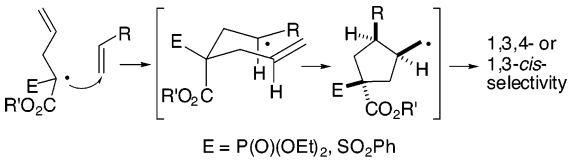

FIGURE 1. Origin of the diastereoselectivity in the reaction with **1** or **2**.

complete diastereoselectivity (≥30:1) was observed (entry 7). The high diastereoselectivities observed in these reactions should be noted, because in general, the cycloaddition reaction with an allylated active methine radical proceeds in low stereoselectivity.[1,13]

All reactions in Table 1 were performed between −15 and 0 °C, while an increase in the reaction temperature (up to room temperature) resulted in a decrease in the chemical yield of iodomethyl products **3** and **4** because of the formation of methyl derivatives as a side product. The methyl derivatives may be derived by reduction of iodides **3** and **4** by Et_3B.

The relative configuration of the major isomers **3a**, **3c**, and **4c** were determined by NMR analysis (**3a**, **3c**: $^1H-^1H$ NOESY and $^1H-^{31}P$ NOESY) or X-ray analysis (**4c**). These analyses indicate that the alkyl substituents and the phosphonyl or phenylsulfonyl group in the major products of entries 1, 2, 4, and 7 are in cis relationships as shown in Table 1.

The high cis selectivity in the present reaction may be rationalized as shown in Figure 1. The subsequent 5-exo cyclization of the radical intermediate formed by the addition of an allylated active methine radical to an alkene may proceed through a chairlike cyclization model. In the cyclization model, more bulky substituents (alkene part, R substituent at the radical center and the phosphonyl or phenylsulfonyl group) should prefer the equatorial position. Accordingly, the reaction should preferentially give 1,3,4-*cis*- or 1,3-*cis*-cyclopentane derivatives.[14]

Although the exact relative configurations of the major isomers **3b**, **4a**, and **4b** were not determined, we believe that their stereochemistries shown in entries 3, 5, and 6 in Table 1 are correctly deduced on the basis of the cyclization model shown in Figure 1.

The reactivity of an allylated active methine radical toward an alkene may strongly depend on the kind of electron-withdrawing group. That is, although the reaction of 2-ethyl-1-butene with an allylcyanoacetate radical prepared from methyl 1-cyano-2-(iodomethyl)cyclopropane-1-carboxylate was also investigated under the same conditions, no cycloaddition product was obtained.

In conclusion, we have succeeded in the development of stereoselective iodine atom transfer [3 + 2] cycloaddition reaction with alkenes using 1-diethylphosphonyl- or 1-phenylsulfonyl-2-(iodomethyl)cyclopropane-1-carboxylate as novel unsymmetrical allylated active methine radical precursors. The present reaction should provide a powerful means for the one-step synthesis of cyclopentane derivatives having various functional groups. Furthermore, it should be noted that the cyclopentane derivatives having a maximum of three chiral carbons are obtained with high diastereoselectivity.

(13) Although the reaction of 1-alkene with a symmetrical allylated malonate radical has been investigated by several groups, the diastereoselectivity is not so high (diastereomer ratio = 2.5:1−5:1, see ref 1b,c,f).

(14) As described in our previous paper (ref 2a,b), in the reaction of dimethyl 2-(iodomethyl)cyclopropane-1,1-dicarboxylate with 1-alkenes, moderate or relatively high 3,4-cis selectivity (5.6:1−11.2:1) between 3-iodomethyl and 4-alkyl groups has been observed.

Experimental Section

***trans*- and *cis*-1-Diethylphosphonyl-2-(iodomethyl)cyclopropane-1-carboxylic Acid Ethyl Ester (1 and 1′). 1** and **1′** were prepared through iodocarbocyclization of allyl phosphonoacetate, which was previously reported by our group. NMR data of **1** and **1′** coincided with those reported in our previous paper.[4c]

***trans*- and *cis*-2-Iodomethyl-1-(phenylsulfonyl)cyclopropane-1-carboxylic Acid Methyl Ester (2 and 2′).** Under an Ar atmosphere, to a solution of methyl allyl(phenylsulfonyl)-acetate (2.54 g, 10 mmol) in THF (70 mL) was added NaH (60% assay, 480 mg, 12 mmol) at 0 °C. After the mixture was stirred for 10 min, I_2 (2.54 g, 10 mmol) was added, and then the mixture was refluxed for 15 h. The mixture was poured into 2% HCl solution, and the products were extracted with AcOEt. The AcOEt extracts were washed with aqueous $Na_2S_2O_3$ solution, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 3) gave a mixture of **2** and **2′**. Further purification by recrystallization (CCl_4) of the mixture gave **2** (2.13 g, 56%, precipitated crystals) and **2′** (152 mg, 4%, crystals from supernatant liquor). **2**: white solid; mp 87 °C; IR (KBr) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, J = 7.3 Hz, 2H), 7.66 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.3 Hz, 2H), 3.70 (s, 3H), 3.44 (dd, J = 6.7, 10.5 Hz, 1H), 3.16 (t, J = 10.5 Hz, 1H), 2.79 (dddd, J = 6.7, 7.9, 9.7, 10.5 Hz, 1H), 2.40 (dd, J = 5.6, 9.7 Hz, 1H), 1.88 (dd, J = 5.6, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 165.0, 139.4, 133.8, 129.5, 128.7, 53.0, 52.9, 32.7, 23.7, −0.6; MS (*m*/*z*) 403 (M^+ + Na). Anal. Calcd for $C_{12}H_{13}ISO_4$: C, 37.91; H, 3.45. Found: C, 37.97; H, 3.49. **2′**: white solid; mp 102 °C; IR (KBr) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, J = 7.3 Hz, 2H), 7.66 (t, J = 7.3 Hz, 1H), 7.56 (t, J = 7.3 Hz, 2H), 3.98 (dd, J = 10.0, 11.0 Hz, 1H), 3.73 (dd, J = 4.7, 10.0 Hz, 1H), 3.59 (s, 3H), 2.56 (ddt, J = 4.7, 9.0, 11.0 Hz, 1H), 2.08−2.15 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 166.3, 140.3, 133.8, 128.9, 128.8, 54.5, 53.0, 36.0, 24.0, −0.1; MS (*m*/*z*) 403 (M^+ + Na); HRMS calcd for $C_{12}H_{13}NaISO_4$ (M^+ + Na) 402.9471, found 402.9477.

General Procedure of Radical Iodine Atom Transfer Cycloaddition with Alkyl-Substituted Alkenes. Under an Ar atmosphere, to a solution of *trans*-2-iodomethyl-1-(phenylsulfonyl)cyclopropane-1-carboxylic acid methyl ester **2** (350 mg, 0.92 mmol), 1-hexene (0.24 mL, 1.84 mmol), and $Yb(OTf)_3$ (570 mg, 0.92 mmol) in CH_2Cl_2 (7 mL) was added Et_3B (0.92 mL, 1 M hexane solution) at −15 °C. Dry air (10 mL) was subsequently introduced with a syringe. After being stirred for 6 h between −15 and 0 °C, the mixture was poured into aqueous $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt extracts were washed with brine, dried over $MgSO_4$, and evaporated to dryness. Purification of the residue by column chromatography (hexane/AcOEt = 5) and subsequent MPLC (hexane/AcOEt = 5) gave a mixture of **4a** and the minor diastereomer in a ratio of 21:1 (278 mg, 65%).

***(1R*,3S*,4R*)*-3-Butyl-4-iodomethyl-1-(phenylsulfonyl)-cyclopentane-1-carboxylic Acid Methyl Ester (4a). 4a**: colorless oil; IR (neat) 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (d, J = 7.4 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.4 Hz, 2H), 3.65 (s, 3H), 3.28 (dd, J = 5.6, 9.4 Hz, 1H), 3.22 (t, J = 9.4 Hz, 1H), 2.53−2.64 (m, 2H), 2.37−2.52 (m, 2H), 2.27 (dd, J = 10.0, 13.5 Hz, 1H), 1.96 (m, 1H), 1.21−1.43 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.0, 136.8, 134.1, 129.8, 128.8, 77.9, 53.3, 44.6, 42.1, 38.2, 35.8, 30.2, 28.6, 22.7, 14.0, 7.9; MS

(*m*/*z*) 465 ($M^+ + H^+$). Anal. Calcd for $C_{18}H_{25}ISO_4$: C, 46.56; H, 5.43. Found: C, 46.70; H, 5.61.

Acknowledgment. This work was partly supported by a Grant-in-Aid for Scientic Research (No. 14572051) from the Ministry of Education, Science, Sports and Culture of Japan.

Supporting Information Available: Experimental procedures and characterization data for products **3a**−**3c**, **4b**, **4c**, and X-ray analytical data of **4c**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035771A