A New and Improved Synthesis of *trans*-1,2-Diiodoalkenes and Their Stereospecific and Highly Regioselective Trifluoromethylation

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Reaction of terminal alkynes with iodine in the presence of CuI (5%) in acetonitrile under reflux for several hours gave the *trans*-1,2-diiodoalkenes in high yields. The trifluoromethylation of these diiodides using $FSO_2CF_2CO_2Me$/CuI/DMF proceeded in excellent yields in a stereospecific and highly regioselective manner.

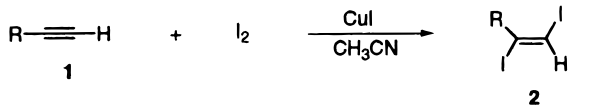
Introduction

Trifluoromethylated compounds remain of great interest in the pharmaceutical and agrochemical industries.[1] Trifluoromethyl-containing compounds are generally synthesized via functional group transformation processes or by use of synthetic building blocks that already contain the trifluoromethyl group.[2] The coupling reaction of the in situ-generated trifluoromethylcopper reagent, CF_3Cu, with alkenyl and aryl halides has been reported to be useful for direct introduction of CF_3 into a molecule.[2] Although there are a number of methods for generating CF_3Cu as well as studies of its reaction with organic halides,[3] the stereochemistry of the reaction has been less studied. In this paper we report the results of the stereospecific and highly regioselective trifluoromethylation of *trans*-1,2-diiodoalkenes using the convenient trifluoromethylating reagent $FSO_2CF_2CO_2Me$/CuI/DMF.[3c] A new and improved method of preparation of such diiodides from terminal alkynes is also reported.

Results and Discussion

Improved Method for Synthesizing *trans*-1,2-Diiodoalkenes from Terminal Alkynes. The iodination of alkynes has been reported to be stereospecific, with only *trans*-adducts being obtained.[4] Although the iodination of alkynes using I_2 in $CHCl_3$ or chlorobenzene has been reported to give the *trans*-diiodides in almost quantitative yields,[4] we found the reaction to be very slow, with low conversion. A brief report of iodination of terminal alkynes in methanol has also appeared.[5] Al_2O_3 was reported to catalyze the iodination of electron rich alkynes, i.e., 1-hexyne,[6] but we found the reaction not to work well for electron-deficient alkynes. For example, when $CH{\equiv}CCO_2H$ was allowed to react with I_2 in hexane in the presence of Al_2O_3, diiodide *E*-$CHI{=}CICO_2H$ was obtained in only 23% yield.

Table 1. Reaction of I_2 with Alkynes in the Presence of CuI (5%) in CH_3CN



alkyne	R	temp (°C)	time (h)	**2** (%)[a]
1a	C_6H_5	60	3.5	**2a** (95)
1b	*p*-MeC_6H_4	60	3	**2b** (95)
1c	*n*-C_4H_9	80	5	**2c** (90)
1d	CO_2Et	80	10	**2d** (85)

[a] Isolated yields based on the alkynes.

We found cuprous iodide (CuI) to be a very good catalyst for the iodination of terminal alkynes. Treatment of alkynes **1** with 1.5 equiv of I_2 in the presence of 5% CuI in acetonitrile under appropriate reaction conditions led to the formation of diiodides **2** in excellent yield (Table 1).

From the results given in Table 1, it can be seen that both electron-rich and electron-deficient alkynes gave very good yields, although the latter needed a longer reaction time and higher temperature. It should be noted that no over-iodinated products, i.e., RCI_2CI_2H or alkynyl iodides, were detected. The presence of CuI was critical; in its absence, the reaction was slow.

The *trans* structures of the diiodides were assigned on the basis of their ^1H NMR spectra. Such spectra were identical to those reported in the literature for the *E*-isomers.[4]

Monotrifluoromethylation of *trans*-1,2-Diiodoalkenes. It was well-known that, in the reaction of CF_3Cu with alkenyl and aryl halides, the iodides are more reactive than the corresponding bromides, and the bromides are much more reactive than the corresponding chlorides,[3c] but no one has studied the relative reactivities

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Table 2. Reaction of 1,2-Diiodoalkenes 1a−d with 2.5 Equiv of $FSO_2CF_2CO_2Me$ in the Presence of CuI (10%) in DMF

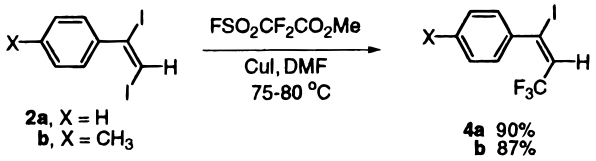
diiodide	R	temp (°C)	time (h)	product (%)[a]
1a	C_6H_5	75−80	8	**7a** (91)
1b	*p*-Me-C_6H_4	75−80	10	**7b** (90)
1c	*n*-C_4H_9	75−80	9	**7c** (80)
1d	CO_2Et	75−80	12	**7d** (72)

[a] Isolated yields based on the diiodides.

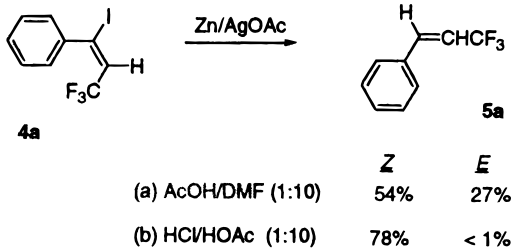
of dihalides that have two identical halogen atoms in different structural environments.

With diiodoalkenes of the general structure **2** now readily available with iodine substituents at electronically distinctive positions, it was of interest to investigate the possibility of selective trifluoromethylation. Structure−reactivity relationships for vinylic iodine substitution by trifluoromethylcopper reagents are not well defined. Thus it was believed that a study of regioselectivity in our series of diiodides might provide some mechanistic insight into this reaction. Moreover, the products of such monotrifluoromethylation, retaining one iodo substituent, will be ideal substrates for further structural elaboration.

Reaction of 1.1 equiv of $FSO_2CF_2CO_2Me$ (**3**) with 1 equiv *trans*-α,*β*-diiodostyrene, **2a**, in the presence of 10% molar CuI in *N*,*N*-dimethylformamide under N_2 atmosphere at 75−80 °C gave a single trifluoromethylated product in 90% yield. When the reaction was monitored

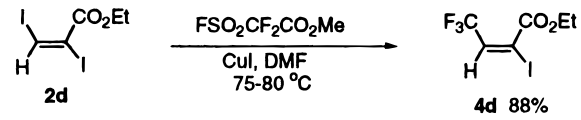


by ^{19}F NMR, it was observed that as the signal at −103 ppm (FSO_2CF_2CO2Me) decreased, a new doublet (−58.2 ppm, J = 7 Hz) increased, with no other fluorine signals appearing during the reaction. The coupling constant of the product (7 Hz) is a typical value for $^3J_{F-H}$ of PhCI=C*HCF*$_3$; therefore, the product was assigned to be PhCI=CHCF$_3$ (**4a**). The configuration of the double bond was designated *E* based on the coupling constant between the *cis*-vinyl protons ($^3J_{H,H}$ = 12.3 Hz) of the *reduced* product PhC*H*=C*H*CF$_3$ (**5a**). When product **4a** was reduced to **5a** using Zn/AgOAc in DMF in the presence of acetic acid (AcOH/DMF = 1:10(v/v)), *two* isomers were obtained in a ratio of *Z*/*E* = 2:1. The configurations of the reduced products were easily assigned based on the coupling

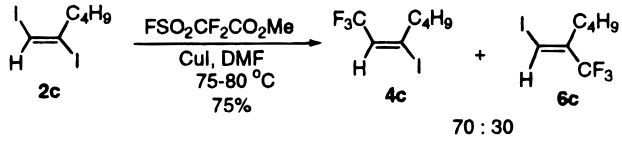


constants of the two vinylic protons, comparing them with those reported in the literature.[7] (For the *E*-isomer, the coupling constant of C*H*=C*H* is 16.1 Hz, whereas the *Z*-isomer has a $^3J_{H-H}$ = 12.3 Hz.) When the reduction of PhCI=CHCF$_3$ was carried out in AcOH/HCl (10:1(v/v)) using Zn/AgOAc as reducing agent, *a stereospecific reduction of the C−I bond was observed*, with only the *Z*-isomer being obtained. On the basis of these results, the *E*-configuration was assigned to product **4a**.

Similar results were obtained for diiodides **1b** and **1d**, as indicated above and below.



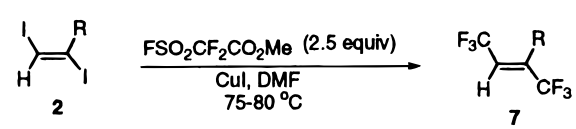
In contrast, when the *E*-1,2-diiodohex-1-ene (**1c**) was allowed to react with 1.1 equiv of $FSO_2CF_2CO_2Me$ under similar reaction conditions, the reaction lost its regiospecificity, with the two iodo substituents being competitive in their respective reactions with CF_3Cu. Only monosubstitution was observed, with the terminal iodo substituent still being more reactive than the internal one (ratio = 70:30).



Although it is reported that in the trifluoromethylation of aryl or alkenyl iodides,[3c] either CuI or CuBr can be used as catalyst, we have found that, in the present examples, *only CuI* is effective as the reaction catalyst. When CuBr was used as catalyst in the reactions, only deiodination of the diiodides occurred to regenerate alkyne. The observed ineffectiveness of CuBr in the current study probably derives from the lower nucleophilicity of bromide versus iodide, which apparently slows the formation of CF_3Cu sufficiently to allow the competitive deiodination to dominate in the reaction with CuBr, but not in the reaction with CuI.

It should also be noted that although the reaction of diiodides with CF_3Cu reagent occurred with great efficiency and selectivity, when CH_3Cu was used in the reaction, *no* analogous coupling was observed. Thus, when CH_3Cu, prepared from MeLi and CuI, was allowed to react with **2a** at −78 °C, only (PhC≡C)$_2$ was obtained. When catalysis by CuCN was attempted, no CF_3Cu chemistry was observed, probably again because of the relatively low nucleophilicity of cyanide ion. Instead a complicated reaction mixture was obtained, with nonselective CN coupling being the major observed reaction.

Preparation of Bis-trifluoromethylated Alkenes. Although only monotrifluoromethated products were obtained when using 1.1 equiv of $FSO_2CF_2CO_2Me$, the remaining iodine substituent is by no means inert to trifluoromethylcopper. When *2.5* equiv of $FSO_2CF_2CO_2Me$ was used in the reaction, both iodine substituents were readily replaced, presumably stereospecifically, to give a single product in each case.



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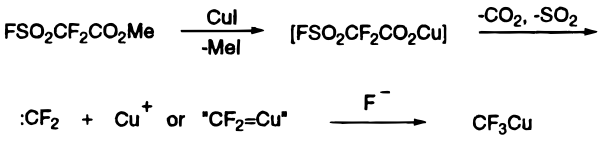
The results given in Table 2 above indicate that all of the diiodides are converted smoothly to the *trans*-1,2-bis-trifluoromethylalkenes, **7a**−**d**, in good to excellent yields.

Mechanistic Discussion

The mechanism of generation of CF_3Cu from $FSO_2CF_2CO_2Me$ has been discussed previously.[3c] Ambiguity exists regarding the nature of specific intermediates formed after decarboxylation and prior to formation of CF_3Cu,



although it is believed that CF_3Cu is likely in equilibrium with the CF_2 carbene complex, $(CF_2{=}Cu)^+F^-$, and that the reactivity of such species are dependent upon the nature of the CuX counterion.[8]

In a study of the reaction of *para*-substituted aryl iodides with CF_3CO_2Na/CuI, Chambers reported a ρ value of +0.46, indicating that such reactions are assisted by electron-withdrawing substituents on the substrate aryl iodide.[3d] Our results are consistent with this general picture, since the aryl and carbethoxy substituents of **1a**, **1b**, and **1d** are anion-stabilizing, whereas the *n*-Bu substituent of **1c** is not.

Conclusions

A new and highly efficient, stereospecific synthesis of *trans*-1,2-diiodoalkenes from terminal alkynes by addition of I_2 in the presence of catalytic CuI in acetonitrile has been presented. In cases where the diiodoalkene is substituted by an aryl or carboethoxy group, as in **2a**, **2b**, and **2d**, it is possible to replace the iodo substituent at the terminal position by a trifluoromethyl group in a regio- and stereospecific manner, using the convenient in situ CF_3Cu reagent obtained from $FSO_2CF_2CO_2Me$/CuI/DMF. The reported chemistry provides synthetic chemists with a new approach to preparing *trans*, *vicinal* trifluoromethyl iodo alkenes, which are potentially useful fluorinated synthetic intermediates.

Experimental Section

Typical Procedure for the Iodination of Alkynes. Into a 150 mL round-bottomed flask was added a mixture of acetonitrile (50 mL), alkyne (50 mmol), I_2 (75 mmol), and CuI (2.5 mmol). The mixture was stirred vigorously under reflux for 3−5 h. After the reaction was over, the mixture was poured into 200 mL of hexane. The resulted solution was washed with $Na_2S_2O_4$ (10% aqueous solution) and then with brine to pH = 7, dried over $CaCl_2$, and concentrated by rotoevaporation. Purification by flash column chromatography gave the desired product.

(*E*)-1,2-Diiodostyrene (2a):[4] ^{1}H NMR δ 7.25 (s, 5H), 7.16 (s, 1H).

(*E*)-1,2-Diiodo-*p*-methylstyrene (2b):[4] ^{1}H NMR δ 2.39 (s, 3H), 7.20 (d, J = 7.6 Hz, 2H), 7.26 (s, 1H), 7.31 (d, J = 7.6 Hz, 2H).

Ethyl (*E*)-2,3-diiodobut-2-enoate (2c):[4] ^{1}H NMR δ 1.34 (t, J = 7.2 Hz, 3H), 4.29 (q, J = 7.2 Hz, 2H), 7.66 (s, 1H).

(*E*)-1,2-Diiodohexene (2d):[4] ^{1}H NMR δ: 0.93 (t, J = 7.2 Hz, 3H), 1.35 (h, J = 7.2 Hz, 2H), 1.51 (p, J = 7.2 Hz, p, 2H), 2.49 (t, J = 7.2 Hz, 2H), 6.78 (s, 1H).

Typical Procedure for the Preparation of Monotrifluoromethylated Compounds. Into a 50 mL three-necked, round-bottomed flask, equipped with magnetic stirrer, thermometer, and condenser with a gas outlet on the top was added a mixture of dry DMF (20 mL), **2** (10 mmol), $FSO_2CF_2CO_2Me$ (11 mmol), and CuI (0.5 mmol). The mixture was then heated to 75−80 °C with stirring. After the reaction was over (monitored by ^{19}F NMR), the reaction mixture was cooled to room temperature and extracted with hexane (3 × 40 mL). The combined hexane solution was then washed with brine and dried over $CaCl_2$. Distillation gave the desired products.

(*E*)-1-Iodo-1-phenyl-3,3,3-trifluoropropene (4a): bp 105−106 °C/25 mmHg. ^{1}H NMR δ 6.49 (q, J = 7.2 Hz, 1H), 7.19 (s, 5H); ^{19}F NMR δ −58.27 (d, J = 7.2 Hz). HRMS calcd for $C_9H_6F_3I$: 297.9466, found: 297.9461.

(*E*)-1-Iodo-1-(*p*-methylphenyl)-3,3,3-trifluoropropene (4b): bp 123 °C/25 mmHg. ^{1}H NMR δ 1.85 (s, 3H), 6.10 (q, J = 7.2 Hz, 1H), 6.64 (d, J = 7.2 Hz, 2H), 6.73 (d, J = 7.2 Hz, 2H). ^{19}F NMR δ −58.16 ppm (d, J = 7.2 Hz). HRMS calcd for $C_{10}H_9F_3I$: 311.9623, found: 311.9588.

Ethyl (*E*)-2-iodo-4,4,4-trifluorobut-2-enoate (4d): bp 50 °C/25 mmHg. ^{1}H NMR δ 1.30 (t, J = 7.2 Hz, 3H), 4.29 (q, J = 7.2 Hz, 2H), 6.49 (q, J = 7.2 Hz, 1H); ^{19}F NMR δ −61.92 (d, J = 7.2 Hz). HRMS calcd for $C_6H_6F_3IO_2$: 293.9365, found: 293.9359.

(*E*)-3-Iodo-1,1,1-trifluorohex-2-ene (4c) and (*E*)-1-iodo-2-(trifluoromethyl)hexene (6c). A mixture of (*E*)-$CF_3CH{=}CIC_4H_9$ (**4c**) and (*E*)-$CHI{=}C(CF_3)C_4H_9$ (**6c**) was obtained from the reaction (*E*)-$CHI{=}CIC_4H_9$ with $FSO_2CF_2CO_2Me$: ^{1}H NMR for (*E*)-$CF_3CH{=}CIC_4H_9$: δ 0.92 (t, J = 7.2 Hz, 3H), 1.34 (m, 2H), 1.52 (m, 2H), 2.59 (t, J = 7.5 Hz, 2H), 6.36 (q, J = 7.8 Hz, 1H); ^{19}F NMR δ −58.44 (d, J = 7.8 Hz); ^{1}H NMR for (*E*)-$CHI{=}C(CF_3)C_4H_9$ δ 0.93 (t, J = 6.9 Hz, 3H), 1.25 (m, 2H), 1.43 (m, 2H), 2.23 (t, J = 8.7 Hz, 2H), 7.16 (s, 1H); ^{19}F NMR δ −67.023(s). HRMS calcd for $C_7H_{10}F_3I$: 277.9779, found: 277.970.

Reduction of (*E*)-PhCI=CHCF$_3$ (4a) in DMF. Into a 50 mL round-bottomed flask was added a mixture of DMF (10 mL), AcOH (1 mL), **4a** (1.5 g), Zn dust (0.6 g), and AgOAc (0.1 g). The mixture was then stirred at room temperature under N_2 for 8 h. After the reaction was over, the reaction mixture was filtered, and the filtrate was mixed with 30 mL of hexane and 10 mL of H_2O. The organic layer was separated, and the water solution was extracted with hexane (20 mL × 3). The combined organic solution was washed with water (10 mL × 3), dried, and concentrated. Distillation (70 °C/25 mmHg) gave 0.7 g (81%) $PhCH{=}CHCF_3$ ((*Z*)- and (*E*)-**5a**) with the ratio of *Z*/*E* = 2:1).

(*E*)-1-Phenyl-3,3,3-trifluoropropene ((*E*)-5a):[7] ^{1}H NMR δ −6.20 (dq, J = 16.1 Hz, 7.3 Hz, 1H), 7.30 (m, 6H); ^{19}F NMR δ −62.81 (d, J = 7.3z).

(*Z*)-1-Phenyl-3,3,3-trifluoropropene ((*Z*)-5a): ^{1}H NMR δ 5.75 (dq, J = 7.1 Hz, 12.3z), 6.92 (d, J = 12.3 Hz, 1H), 7.36 (m, 5H); ^{19}F NMR δ −58.14 (d, J = 7.1 Hz).

Reduction of (*E*)-PhCI=CHCF$_3$ in AcOH. (*E*)-$PhCI{=}CHCF_3$ (1.5 g, 5 mmol), Zn (1.2 g, 20 mmol), and AgOAc (0.1 g, 0.6 mmol) were mixed together in AcOH (10 mL). Under vigorous stirring 1 mL of concentrated HCl (37%) was added dropwise over a 5 min period. The mixture was further stirred for 5 min. ^{19}F NMR indicated the reaction was over, and only a doublet at −58.2 ppm appeared. Normal workup gave pure (*Z*)-$PhCH{=}CHCF_3$ ((*Z*)-**5a**) in 78% yield.

General Procedure for the Preparation of 1,2-Bis-(trifluoromethyl)alkenes 7a−d. Into a 50 mL three-necked, round-bottomed flask, equipped with magnetic stirrer, thermometer, and condenser with a gas outlet on the top, was added a mixture of DMF (20 mL), diiodide (**1a**−**d**) (10 mmol), $FSO_2CF_2CO_2Me$ (25 mmol), and CuI (0.5 mmol). The mixture was then heated to 75−80 °C under stirring. After the reaction was over (monitored by ^{19}F NMR), the reaction mixture was distilled under reduced pressure (40 mmHg). The distillate was added to 50 mL of ice−water, and an organic layer separated. After the organic layer was separated, the water solution was

(8) Yang, Z.-Y.; Wiemers, D. M.; Burton, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 4402.

extracted with CH_2Cl_2 (5 mL × 3), and the combined organic solution was washed with H_2O (10 mL × 3) and dried. Distillation gave the desired product (**7a**−**d**).

(*E*)-1,1,1,4,4,4-Hexafluoro-2-phenylbut-2-ene (7a): bp 58−60 °C/25 mmHg. ^{1}H NMR δ 6.48 (q, J = 7.2 Hz, 1H), 7.30 (t, J = 7.2 Hz, 2H), 7.41 (m, 3H); ^{19}F NMR δ −58.63 (d, J = 7.2 Hz, 3F), −68.87 (s, 3F). HRMS calcd for $C_{10}H_6F_6$: 240.0373, found: 240.0321.

(*E*)-1,1,1,4,4,4-Hexafluoro-2-(*p*-methylphenyl)but-2-ene (7b): bp 79−82 °C/25 mmHg. ^{1}H NMR δ 1.87 (s, 3H), 5.94 (q, J = 7.2 Hz, 1H), 6.66 (d, J = 7.2 Hz, 2H), 6.71 (d, J = 7.2 Hz, 2H); ^{19}F NMR δ −58.57 (d, J = 7.2 Hz, 3F), −68.89 (s, 3F). HRMS calcd for $C_{11}H_9F_6$: 254.0530, found: 254.0550.

Ethyl (*E*)-4,4,4-trifluoro-2-(trifluoromethyl)but-2-enoate (7c): bp 112 °C. ^{1}H NMR δ 1.33 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.2 Hz, 2H), 6.44 (q, J = 6.9 Hz); ^{19}F NMR δ −61.99 (d, J = 6.9 Hz, 3F), 66.39 (s, 3F). HRMS, M^+ − EtO calcd for C_5HF_6O: 190.9932, found: 190.9936.

(*E*)-1,1,1-Trifluoro-3-(trifluoromethyl)hept-2-ene (7c): bp 71−72 °C. ^{1}H NMR δ 0.71 (t, J = 7.3 Hz, 3H), 1.10 (h, J = 7.3 Hz, 2H), 1.32 (p, J = 7.3 Hz), 2.13 (t, J = 7.3 Hz, 2H), 5.87 (q, J = 7.8 Hz, 1H); ^{19}F NMR δ −59.67 (d, J = 7.8 Hz, 3F), 69.09 (s, 3F). HRMS, M^+ − 1 calcd for $C_8H_9F_6$: 219.0608, found: 219.0595.

Acknowledgment. Support of this work in part by the National Science Foundation is acknowledged with thanks.

Supporting Information Available: ^{1}H and ^{19}F NMR spectra of all previously unreported compounds (**4a**−**d, 6c, 7a**−**d**) (16 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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