Alkynylation of C−H Bonds via Reaction with Acetylenic Triflones[1]

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In connection with our program investigating the chemistry of the sulfone functional group, we had occasion to prepare acetylenic triflones **1a,b** (Scheme 1) via the direct reaction of acetylenic anions with triflic anhydride.[2] An exceptional observation attended our attempts to use THF as a solvent for the chemistry of acetylenic triflone **1a**. Simply adding **1a** to THF resulted in an exothermic reaction which produced α-alkynylated tetrahydrofuran in essentially quantitative yield (Table 1, entry 1). Similar reactions with five- and six-membered ethers and sulfides results in the formation of α-functionalized ethers and sulfides in good to excellent yields (Table 1, entries 3−5, 10−13). In contrast, anisole and phenyl isopropyl ether are recovered unchanged from the reaction.[3] For those reactions run in solution, the best compromise solvent appears to be 1,2-dichloroethane.[4] While even this compound undergoes alkynylation, the reaction is quite slow and most substrates are efficiently alkynylated with minimal competitive production of the propargyl chloride (Table 1, entry 14).[5]

In an effort to probe the regiospecificity of the reaction, the substrates of Figure 1 were similarly investigated. Lower regiospecificities were observed upon initiation with AIBN at reflux (procedure B) as compared to reaction at 25 °C without added initiator (procedure A).

Even more astounding is the observation that *unactivated hydrocarbons are alkynylated when heated in the presence of **1a,b*** and AIBN or via photochemical activation. Cyclopentane, cyclohexane, cycloheptane,[6] *cis*-1,4-dimethylcyclohexane (Figure 1),[7] 2,3-dimethylbutane, adamantane, and norbornane[8] afford the products shown in Table 1 (entries 6, 7, 9, 15, 17, 19) while cubane, which has an olefin-like hybridization of ∼31% s character,[9] does not undergo successful alkynylation.

Scheme 1

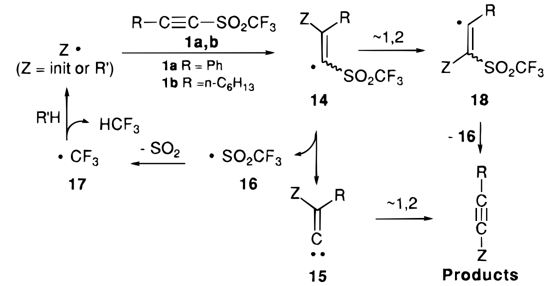
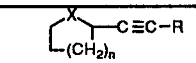
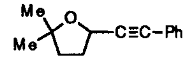
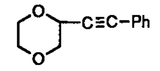
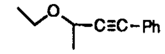
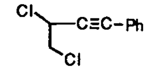
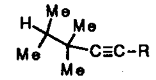
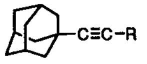
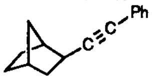


Table 1. Reaction with Acetylenic Triflones **1a,b**

Entry	Cond[a]	Triflone	Product	Yield
1	A, 3h B, 1h C, 1h	1a	 X=O, n=1, R=Ph	92% 90% 88%
2	B, 5h	1b	X=O, n=1, R=n-C_6H_{13}	61%
3	B, 1.5h	1a	X=O, n=2, R=Ph	88%
4	A, 24h C, 10h	1a	X=S, n=1, R=Ph	59% 71%
5	C, 10h	1a	X=S, n=2, R=Ph	65%
6	D, 5h	1a	X=CH_2, n=1, R=Ph	63%
7	B, 2h D, 1h	1a	X=CH_2, n=2, R=Ph	83% 72%
8	B, 40h	1b	X=CH_2, n=2, R=n-C_6H_{13}	62%
9	B, 7h	1a	X=CH_2, n=3, R=Ph	64%
10	B, 15h	1a		92%
11	B, 2h	1a		87%
12	A, 18h B, 2h	1a	t-Bu−O−CH_2-C≡C−Ph	NR 87%
13	A, 3h	1a		90%
14	B, 20h	1a		29%
15	B, 10h	1a	 R=Ph	78%
16	B, 24h	1b	R=n-C_6H_{13}	49%
17	C, 24h	1a	 R=Ph	60%
18	C, 5d	1b	R=n-C_6H_{13}	40%*
19	C, 24h	1a		25%

[a] Procedure A: neat substrate, probable trace peroxides, 25 °C. Procedure B: neat substrate, ∼20% AIBN, reflux. Procedure C: 1.1−1.2 equiv of substrate, AIBN, $ClCH_2CH_2Cl$, reflux. Procedure D: neat substrate, Rayonet reactor, *hν* 254 nm, 25 °C. *Based upon 50% recovered **1a**.

The reaction has the characteristics of a radical process. Highly purified THF does not react with alkynyl triflone **1a** when heated in an argon atmosphere, but warming in the presence of AIBN, peroxides, or small amounts of oxygen serves to initiate the process. Conversely, addition of BHT or *m*-dinitrobenzene prevents the reaction from occurring.

While mechanistic experiments are underway, the tentative hypothesis shown in Scheme 1 appears to be consistent with the information currently available. The reaction is postulated to be initiated ($Z^\bullet$ = init) and propagated ($Z = R'^\bullet$) by addition of a radical to the *β*-carbon of acetylenic triflones **1a,b** thereby

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[1] Syntheses via Vinyl Sulfones. 61. Triflone Chemistry 5.

[2] Acetylenic triflones have traditionally been prepared in 50−70% yield by addition of triflic anhydride to a solution of acetylenic anion (Hanack, M.; Wilhelm, B.; Subramanian, L. R. *Synthesis* **1988**, *88*, 592−595); however, we have found that *inverse addition* substantially improves the yield (J. Xiang, A. Mahadevan, P. L. Fuchs, submitted for publication).

[3] Acetylenic triflones have been previously reported to react with alcohols, DMF, and DMSO: (a) Massa, F.; Hanack, M.; Subramanian, L. R. *J. Fluorine Chem.* **1982**, *19*, 601. (b) Hanack, M.; Willhelm, B. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1057.

[4] While Freon 112 and perfluorohexane are unreactive with **1a**,**b**, they do not accommodate clean alkynylation reactions.

[5] The 1,2-dichloroethane adduct (Table 1, entry 14) is easily detected as a distinctive pink-staining UV-active spot when visualized on silica TLC using acidic ethanolic anisaldehyde reagent. **Note Added in Proof**: CH_3CN is also a good reaction solvent. Adamantane gives 81% product with acetylenic triflone **1a** (compare Table 1, entry 17).

[6] When this reaction was conducted under the photolytic conditions (condition D), a 1:1 mixture of cycloheptylphenylacetylene and compound **22** was produced in 80% yield. Examination of the crude product from the thermal reaction (condition B) reveals only traces of compound **22**. Apparently the cycloheptyl radical undergoes partial oxidation to cycloheptene (**20**), which then produces **22** as shown in Scheme 2. No evidence for similar products was seen in the reactions of cyclopentane or cyclohexane.

[7] Both products **8** and **9** are one major (>3:1) diastereomer. The stereochemical assignment has yet to be undertaken, but on the basis of mechanistic arguments (axial attack from the most stable radical intermediate), it is expected that **8** bears the *trans*-dimethyl configuration, while **9** has the *trans*-methyl/alkynyl geometry.

[8] Radical reactions of norbornane are known to occur at the secondary center because of the greater strain associated with the formation of the bridgehead radical via abstraction of the tertiary hydrogen (see ref 18). The ^{13}C NMR of the product uniquely defines the regiochemistry, while decoupling of the proton spectra is indicative of the exostereochemistry.

[9] Eaton, P. E.; Galoppini, E.; Gilardi, R. *J. Am. Chem. Soc.* **1994**, *116*, 7588.

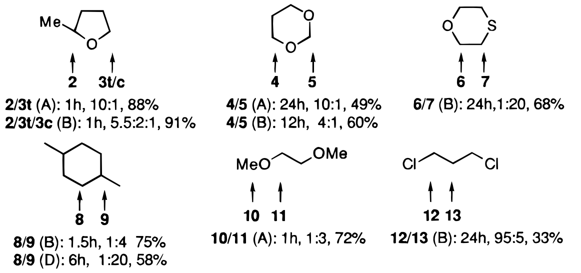


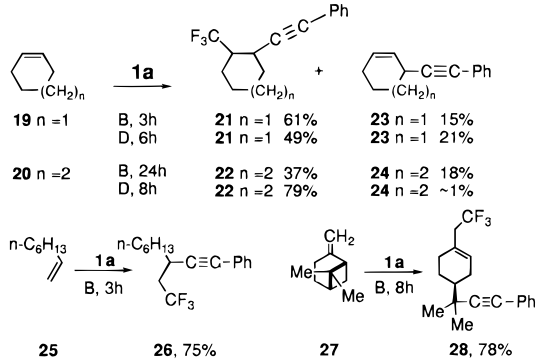
Figure 1. Regiospecificity studies.

generating α-((trifluoromethyl)sulfonyl)vinyl radical **14**, which fragments to vinylidene carbene **15** and (trifluoromethyl)sulfonyl radical **16**. Vinylidene carbenes **15** are well-known to undergo the Fritch−Buttenberg−Weichell rearrangement to afford acetylenes.[10] An alternative mechanism involves either direct production of β-((trifluoromethyl)sulfonyl)vinyl radical **18**[11] or rearrangement of **14** to this species prior to scission of the carbon−sulfur bond. Completion of the process involves the known fragmentation[12] of (trifluoromethyl)sulfonyl radical **16** to sulfur dioxide and the electrophilic trifluoromethyl radical **17**, which propagates the chain by abstraction of a hydrogen atom from the reaction substrate.[13]

In retrospect, one can appreciate the synergistic interplay of effects which renders the acetylenic triflone exquisitely competent to effect the radical alkynylation sequence. The extremely electron-deficient sp-hybridized alkyne moiety engenders efficient trapping of all radical intermediates *except for the trifluoromethyl radical* (BDE $H-CF_3$ =107 kcal/mol), whose own electrophilic character, combined with its minuscule steric requirement, results in C−H abstraction, thereby ensuring that the radical cascade is efficiently propagated.

On the basis of the mechanism shown in Scheme 1, it was expected that treating olefins with reagent **1a** would effect a conjugate trifluoromethyl-alkynylation reaction instigated by addition of the trifluoromethyl radical.[14,15] Conducting the reaction of acetylenic triflone **1a** with either neat cyclohexene, cycloheptene, or 1-octene activated by AIBN provided trifluoromethylated alkyne adducts **21**, **22**,[16] and **26**[17] in addition to minor products (**23**, **24**) from allylic hydrogen abstraction and some higher molecular weight materials apparently resulting from competitive trapping of the alkyl radical by excess olefin. Conducting the same reaction on β-pinene (**27**) produces adduct **28**, which results from trifluoromethyl radical addition followed by scission of the strained cyclobutane moiety and trapping of the tertiary radical by reagent **1a**. Mass spectral examination of the crude reaction mixture fails to reveal evidence for the presence of any 2:1 adduct which might have resulted from competitive reaction of product **28** with reagent **1a** (Scheme 2).

Scheme 2



At present only several reactions have been carried out with octynyl triflone **1b** (Table 1, entries 2, 8, 15, 18). These reactions are slower and somewhat lower-yielding, which may be indicative of the α-addition mechanism (Scheme 1) via intermediate **18** since the *n*-hexyl moiety would be expected to less strongly stabilize the adjacent vinyl radical than would a phenyl group.

Reactions which involve C−H activation with the concurrent formation of a C−C bond are extremely rare.[18] The ease of preparation of alkynyl triflones, combined with the convenience and good yields, promises wide applicability of this new strategy. Efforts to further delineate the scope and to improve the specificity of this new alkynylation protocol are being vigorously pursued.

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Supporting Information Available: ^{1}H and ^{13}C NMR of all new compounds (69 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

JA953518P

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(10) Stang, P. J. *Chem. Rev.* **1978**, *78*, 383.

(11) Radical addition to the α-carbon of β-phenylvinyl phenyl sulfone and β-phenylethynyl phenyl sulfone is known: Russell, G. A.; Ngoviwatchai, P. *J. Org. Chem.* **1989**, *54*, 1836 and references cited therein.

(12) (a) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992**, *33*, 1291. (b) Hu, C.-M.; Qing, F.-L.; Huang, W.-Y. *J. Org. Chem.* **1991**, *56*, 2801. (c) Huang, W.-Y.; Hu, L.-Q. *J. Fluorine Chem.* **1989**, *44*, 25. (d) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525.

(13) Medebielle, M.; Pinson, J.; Saveant, J.-M. *J. Am. Chem. Soc.* **1991**, *113*, 6872.

(14) For a set of recent references describing the value of trifluoromethylated organics, see: Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692.

(15) For references describing the addition of trifluoromethyl radicals to olefins, see: (a) Uneyama, K.; Kitagawa, K. *Tetrahedron Lett.* **1991**, *32*, 375. (b) Chen, Q.-Y.; Yang, Z.-Y. *J. Chem. Soc., Chem. Commun.* **1986**, 498.

(16) Compound **21** is assigned trans stereochemistry based upon the dt (J = 4, 10.5 Hz) of the propargylic methine; compound **22** is a single diastereomer, of currently unknown stereochemistry (Scheme 2).

(17) The regiochemistry of **26** is assigned by ^{13}C NMR, which shows a methylene carbon coupled to the adjacent CF_3 group.

(18) For an excellent review on the oxidation of unactivated C−H bonds, see: Crabtree, R. H.; Habib, A. In *Comprehensive Organic Synthesis*; Ley, S. V., Vol. Ed.; Trost, B. M., Fleming, I., Series Eds.; Pergamon Press: New York, **1991**;Vol. 7, pp 1−20.