The Journal of
Organic
Chemistry

VOLUME 55, NUMBER 19 SEPTEMBER 14, 1990

Communications

Copper Azide as a New Reagent for Syn-S_N2 Displacement of γ-Sulfonyloxy α,β-Unsaturated Esters

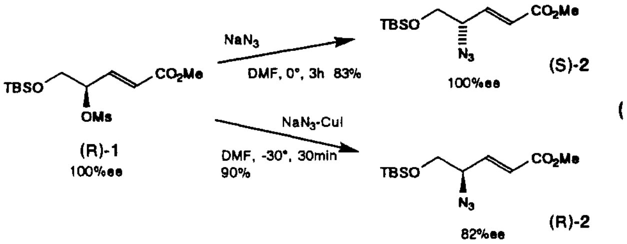
Yoshinori Yamamoto* and Naoki Asao

Department of Chemistry, Faculty of Science, Tohoku University, Sendai 980, Japan

Received May 17, 1990 (Revised Manuscript Received June 26, 1990)

Summary: The reaction of γ-sulfonyloxy α,β-unsaturated esters with NaN_3–CuX(or CuN_3) in polar aprotic solvents such as HMPA, DMSO, and DMF proceeds predominantly in a syn-S_N2 fashion, while the reaction with NaN_3 proceeds in an anti-S_N2 manner.

It is widely accepted that the substitution of sulfonates with metal azides, such as lithium, sodium, and potassium azides, proceeds with inversion of configuration (anti-S_N2).[1] We report that copper azide reacts with γ-sulfonyloxy α,β-unsaturated esters in a syn-S_N2 fashion. As expected, the reaction of (*R*)-**1** with NaN_3 gave (*S*)-**2** in 86% yield with 100% ee. Quite surprisingly, the similar reaction of (*R*)-**1** with NaN_3–CuI produced (*R*)-**2** in 90% yield with 82% ee (eq 1). Both (*S*)- and (*R*)-**2** are precursors for a γ-aminobutyric acid transaminase inactivator, 4-amino-5-hydroxypentanoic acid, whose absolute configuration has not been determined.[2]



(1)

To investigate scope of the syn-S_N2 substitution, we examined the reactions of several sulfonates[3] (Table I).

Table I. Reactions of Sulfonates with Metal Azides

entry	compd	reagent	reaction conditions	yield,[a] %	ratio[b] syn-S_N2: anti-S_N2
					8:**9**
1	**3**	NaN_3–CuI	HMPA, 4 h	86	85:15
2	**3**	NaN_3–CuI	DMSO, 0.5 h	83	82:18
3	**3**	NaN_3–CuBr·SMe_2	DMSO, 0.5 h	88	84:16
4	**3**	NaN_3–NH_4Cl–CuI	DMSO, 0.5 h	85	75:25
5	**3**	NaN_3	DMSO, 5.5 h	42[c]	0:100
6	**3**	CuN_3	DMSO, 0.7 h	81	71:29
					9:**8**
7	4	NaN_3–CuI	HMPA, 4 h	67	84:16
8	4	NaN_3–CuI	DMSO, 0.5 h	89	80:20
					8:**9**
9	**5**	NaN_3–CuI	DMSO, 0.5 h	83	80:20
					10:**11**
10	**6**	NaN_3–CuI	HMPA, 1.5 h	50	76:24
					12:**13**
11	**7**	NaN_3–CuI	DMSO 0.7 h	87	83:17

[a] Isolated yield. [b] Determined by 270-MHz ^1H NMR. [c] The starting material was recovered in 15% yield.

The reaction of **3** with the combination reagents (NaN_3–copper salts) gave the syn-S_N2 product (**8**) in high yields with good stereoselectivity (entries 1–4), although the reaction with NaN_3 in DMSO afforded the anti-S_N2 product in 42% yield (entry 5). The sluggish reaction in NaN_3–DMSO system is due to the low solubility of NaN_3; the reaction is often carried out in an aqueous solution to enhance the speed of substitution. However, the complex reagent NaN_3–CuX is soluble in organic solvents such as

---

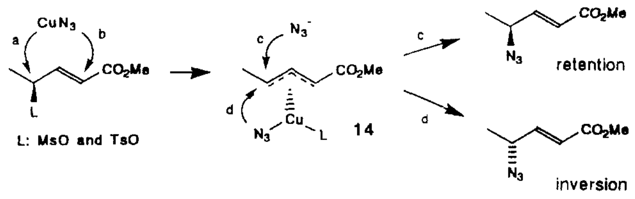
(1) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297 and references cited therein.

(2) Silverman, R. B.; Levy, M. A. *J. Org. Chem.* **1980**, *45*, 815. Davies, J. S., Ed. *Amino Acids and Peptides*; Chapman and Hall: New York, 1985.

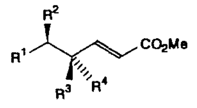
(3) These sulfonates were prepared according to the literatures. (a) **1**: Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883 and references cited therein. (b) **3**, **5**, and **6** were prepared from sorbic acid methyl ester, and also see: Ibuka, T.; Nakao, T.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1986**, *108*, 7420. (c) **4**: Ibuka, T.; Nishii, S.; Yamamoto, Y. *Chem. Express* **1988**, *3*, 53. (d) **7** was prepared from DL-2-phenylpropanal.

0022-3263/90/1955-5303$02.50/0 © 1990 American Chemical Society

Scheme I



DMF, HMPA, DMSO, and MeOH, and the reaction is rapid compared to that of NaN_3 itself. We anticipated that copper azide would be formed in situ by mixing NaN_3 with CuI in the organic solvent. Actually, the reaction of **3** with CuN_3, independently prepared by the reported procedure,[4] gave syn-**8** predominantly in good yield (entry 6). The reaction of **4**, the diastereomer of **3**, with NaN_3–CuI also gave the syn-S_N2 product (**9**) (entries 7 and 8). The substitution proceeded quite smoothly with the tosylate **5** (entry 9). Other leaving groups, such as acetate and phosphonate, are ineffective. The substituent at the δ position did not exert a significant influence upon the diastereoselectivity (entries 10 and 11). The hydroxy-, siloxy-, and alkyl-substituted derivatives produced the syn selectivity. It is also noteworthy that the geometry of the allylic azides obtained in Table I is *E*. The syn-S_N2 displacement was also observed with (4*R**,5*S**)-(*E*)-4-((methylsulfonyl)oxy)-5-(*tert*-butyldimethylsiloxy)-2-hexenophenone, indicating that the present method may be applicable to α,β-unsaturated ketones.



3 R^1=Me, R^2=OTBS, R^3=H, R^4=OMs
4 R^1=Me, R^2=OTBS, R^3=OMs, R^4=H
5 R^1=Me, R^2=OTBS, R^3=H, R^4=OTs
6 R^1=Me, R^2=OH, R^3=OMs, R^4=H
7 R^1=Ph, R^2=Me, R^3=OMs, R^4=H
8 R^1=Me, R^2=OTBS, R^3=H, R^4=N_3
9 R^1=Me, R^2=OTBS, R^3=N_3, R^4=H
10 R^1=Me, R^2=OH, R^3=N_3, R^4=H
11 R^1=Me, R^2=OH, R^3=H, R^4=N_3
12 R^1=Ph, R^2=Me, R^3=N_3, R^4=H
13 R^1=Ph, R^2=Me, R^3=H, R^4=N_3

The structures of **8**–**13** were assigned unambiguously by converting them to the corresponding amino alcohol derivatives. For example, **9** was converted to 4-amino-5-(*tert*-butyldimethylsiloxy)-1-hexanol upon treatment with $LiAlH_4$ followed by hydrogenation over Pd–C. The authentic material was prepared by the allylation of the corresponding imine with allyl-9-BBN,[5] followed by hydration of the double bond with 9-BBN (see the supplementary material).

The syn-S_N2 substitution with copper azide can be accounted for by considering a π-allyl copper intermediate (**14**) (Scheme I). The attack of CuN_3 to the substrate would take place in an anti manner,[6] giving the π-allyl copper complex **14**.[7] The attack of azide ion from the face opposite to the π-allyl copper gives the stereo-retained product (route c). The intramolecular delivery of azide affords the stereo-inverted product (route d). Obviously, the reaction mainly proceeds through the path c. The π-allyl mechanism is also supported by the following observation. Use of excess copper azide (or NaN_3–CuX) produced higher syn stereoselectivity. Normally we used 5–10 equiv of copper azides. The reaction of **3** with 1.7 equiv of NaN_3–CuI in HMPA was relatively sluggish and resulted in low chemical yield and low stereoselectivity; 24% yield and syn/anti = 66/34. Accordingly, the intramolecular delivery must be slow in comparison with the intermolecular attack. Of course, the isomerization of π-allyl ligand may be conceivable for formation of the minor anti product. However, the *E* geometry of the allylic azides would eliminate such possibility. Irrespective of the precise mechanism, the syn-S_N2 substitution[8] opens a door to new syntheses via CuN_3.

Preparation of **8** from **3** is representative. To a suspension of NaN_3 (372 mg, 5.7 mmol) in HMPA (5.7 mL) was added CuI (1.088 g, 5.7 mmol) at room temperature in an Ar atmosphere. After being stirred for 5 min, the mixture became homogeneous and the color of the solution changed to brown. The mixture was stirred for 0.5 h before the addition of a solution of **3** (196 mg, 0.56 mmol) in HMPA (2 mL). After being stirred for 4 h, the mixture was cooled to 5 °C, and a mixture of saturated NH_4Cl (6 mL) and 28% NH_4OH (3 mL) was added. Then, the mixture was allowed to warm to room temperature, and stirring was continued for 15 min. The mixture was extracted with Et_2O. The extract was washed successively with water and brine and dried over anhydrous Na_2SO_4. Removal of the solvents under reduced pressure gave an oily material. Purification by silica gel column chromatography using *n*-hexane–AcOEt (5:1) as an eluant gave the product in 86% yield (144 mg, **8**:**9** = 85:15) along with 15 mg of recovered **3**.

Supplementary Material Available: The spectral data and elemental analyses of 1–13 and the stereochemical determination of the diastereoisomers (18 page). Ordering information is given on any current masthead page.

---

(4) Singh, K. *Trans. Faraday Soc.* **1959**, *55*, 124.

(5) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Ito, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778. Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 814.

(6) The organocopper substitution of allylic carboxylates and sulfonates proceeds through antistereochemistry. For example: (a) Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Lesheski, L.; Goering, H. L. *J. Org. Chem.* **1989**, *54*, 2369. (b) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. The substitution with CuN_3 may take place either path a or path b.

(7) One referee suggests an another possibility for the syn-S_N2 displacement: double inversion via η^1-Cu intermediates. A π-allyl derivative of Cu is frequently proposed as an intermediate of certain alkylation reactions, although its structure is not well characterized: for example, Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721.

(8) During our study, it has been reported that a similar syn-S_N2 displacement takes place with Pd(0) catalysts. Murahashi, S.-I.; Taniguchi, Y.; Imada, Y.; Tanigawa, Y. *J. Org. Chem.* **1989**, *54*, 3292.