THF was added dropwise. The reaction mixture was warmed to room temperature and refluxed for 30 h. Water was then added and the mixture extracted with carbon tetrachloride. Following drying of the combined organic layers over $MgSO_4$ and evaporation of the solvent, the remainder, an oily solid, was purified by column chromatography; $C_{20}H_{15}Cl$, colorless needles, mp 117.5–119 °C (95% ethanol) [lit.[15] mp 117.3–118.9 °C]; ^1H NMR (CCl_4) δ 6.8–7.45 (m); mass spectrum, *m/e* (relative intensity) 290 [M^+ (^{35}Cl), 100], 292 [M^+ (^{37}Cl), 33.5].

(α-Chlorobenzylidene)fluorene (3b): $C_{20}H_{13}Cl$, yellow plates, mp 123–124.5 °C (95% ethanol) [lit.[16] mp 120–122 °C]; ^1H NMR (CCl_4) δ 6.2–7.7 (m); mass spectrum, *m/e* (relative intensity) 288 [M^+ (^{35}Cl), 79.6], 290 [M^+ (^{37}Cl) 28.7].

Clomiphene A and B (as free base; **3c**): pale yellow oil, bp 215 °C (0.55 mm); ^1H NMR ($CDCl_3$) δ 1.05 (m, 6 H) 2.68 (m, 6 H), 4.03 (m, 2 H), 6.6–8.0 (m, 14 H); UV (MeOH) λ_{max} 234, 241;[17] mass spectrum, *m/e* (relative intensity) 405 [M^+ (^{35}Cl), 13.5], 407 [M^+ (^{37}Cl), 4.5]; exact mass calcd for $C_{26}H_{28}ClNO$ *m/e* 405.1861, found *m/e* 405.1859.

1-Chloro-1,3-diphenyl-2-(phenylmethyl)propene (3d): colorless needles, mp 91–92 °C (95% ethanol); ^1H NMR (CCl_4) δ 3.35 (s, 2 H), 3.70 (s, 2 H), 7.0–7.55 (m, 15 H); mass spectrum, *m/e* (relative intensity) 318 [M^+ (^{35}Cl), 43.4], 320 [M^+ (^{37}Cl), 16.3]. Anal. Calcd for $C_{22}H_{19}Cl$: C, 82.87; H, 5.91. Found: C, 83.00; H, 6.05.

1-Chloro-1,2-diphenylpropene (3e): colorless oil, bp 115 °C (0.55 mm); NMR (CCl_4) δ 2.35 (s, 3 H), 6.80–7.25 (m, 10 H); mass spectrum, *m/e* (relative intensity) 228 [M^+ (^{35}Cl), 100.0], 230 [M^+ (^{37}Cl), 30.1]; exact mass calcd for $C_{15}H_{13}Cl$ *m/e* 228.0707, found *m/e* 228.0695.

1-Chloro-1,2-diphenyl-1-butene (3f): colorless oil, bp 123 °C (1.30 mm); ^1H NMR (CCl_4) δ 1.05 (t, 3 H, *J* = 8 Hz), 2.85 (q, 2 H, *J* = 8 Hz), 6.9–7.40 (m, 10 H); mass spectrum, *m/e* (relative intensity) 242 [M^+ (^{35}Cl), 93.1], 244 [M^+ (^{37}Cl), 30.7]; exact mass calcd for $C_{16}H_{15}Cl$ *m/e* 242.0864, found *m/e* 242.0848.

1-Chloro-2,2-bis(3-nitrophenyl)-1-phenylethene (3g): colorless powder, mp 126–127.5 °C [sublimed at 60 °C (0.5 mm)]; ^1H NMR ($CDCl_3$) δ 7.3–8.4 (m); mass spectrum, *m/e* (relative intensity) 380 [M^+ (^{35}Cl), 100], 382 [M^+ (^{37}Cl), 39]. Anal. Calcd for $C_{20}H_{13}ClN_2O_4$: C, 63.08; H, 3.44. Found: C, 62.72; H, 3.66.

1-Chloro-2-(4-cyanophenyl)-1-phenylpropene (3h): colorless powder, mp 74–79 °C, bp 151 °C (0.55 mm); ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 7.1–7.7 (m, 9 H); IR (neat) 2235 cm^{-1}; mass spectrum, *m/e* (relative intensity) 253 [M^+ (^{35}Cl), 98.8], 255 [M^+ (^{37}Cl), 30.7]; exact mass calcd for $C_{16}H_{12}CN$ *m/e* 253.0660, found *m/e* 253.0658. Anal. Calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77. Found: C, 75.72; H, 4.83.

Chlorotrianisene (3i): colorless powder, mp 114–5 °C (MeOH) [lit.[9] mp 113–114 °C]; NMR ($CDCl_3$) δ 3.70 (s, 3 H), 3.75 (s, 3 H), 3.80 (s, 3 H), 6.90 (m, 12 H); mass spectrum, *m/e* (relative intensity) 380 [M^+ (^{35}Cl), 100], 382 [M^+ (^{37}Cl), 38].

Acknowledgment. We acknowledge the assistance of Mr. Frank P. Palopoli of Merrell-Dow for the determination of the *E/Z* content of the isomeric mixture of clomiphene A and B prepared by our method. This investigation was supported in part by an Institutional Grant of the American Cancer Society and a grant by the University of Cincinnati Research Council.

Registry No. **1a**, 773-47-7; **1b**, 17105-65-6; **2a**, 16965-75-6; **2b**, 86457-76-3; **3a**, 18084-97-4; **3b**, 86457-77-4; (*Z*)-**3c**, 15690-55-8; (*E*)-**3c**, 15690-57-0; **3d**, 61507-95-7; (*Z*)-**3e**, 65787-74-8; (*E*)-**3e**, 65787-75-9; (*Z*)-**3f**, 69967-86-8; (*E*)-**3f**, 69967-85-7; **3g**, 86457-78-5; (*Z*)-**3h**, 86457-79-6; (*E*)-**3h**, 86457-80-9; **3i**, 569-57-3; trimethyl phosphite, 121-45-9; benzyl chloride, 100-44-7; 4-anisyl chloride, 824-94-2; benzophenone, 119-61-9; 9-fluorenone, 486-25-9; 4-[2-(diethylamino)ethoxy]benzophenone, 796-77-0; 1,3-diphenyl-2-propanone, 102-04-5; acetophenone, 98-86-2; propiophenone, 93-55-0; 3,3′-dinitrobenzophenone, 21222-05-9; 4-cyanoacetophenone, 1443-80-7; 4,4′-dimethoxybenzophenone, 90-96-0.

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Communications

Interaction of Sulfur Dioxide with 1-Benzyl-1,4-dihydronicotinamide

Summary: Anhydrous sulfur dioxide reacts rapidly with 1-benzyl-1,4-dihydronicotinamide to give a reduced species of sulfur dioxide, possibly HSO_2^-, which can be trapped by reaction with Michael acceptors to give sulfones.

Sir: The ubiquity of sulfur dioxide as an undesirable pollutant is reason for investigation of its interaction with biologically important molecules. Although considerable information is available about the interaction of models for the coenzyme, NAD^+ (nicotinamide adenine dinucleotide), with reduced species of sulfur dioxide such as dithionite[1] or sulfite,[2-4] no studies exist on the interaction of anhydrous sulfur dioxide with dihydronicotinamide models for the reduced coenzyme, NADH, although a reaction with the hypothetical sulfurous acid is described.[4] Removal of water from aqueous solutions of sulfur dioxide regenerates the gas[5] so that in biological systems of low water content the free sulfur dioxide may be an important contributor to the overall toxic effects.

In a recent investigation of the mechanism of the reduction of analogues of NAD^+ by dithionite, evidence was presented for the reaction proceeding via hydride transfer from the sulfoxylate anion, HSO_2^-, to the pyridinium salt to give the 1,4-dihydropyridine and sulfur dioxide.[1] The reverse reaction of sulfur dioxide with the dihydropyridine was excluded.[1] Although this may be true in aqueous media in which these studies were done, where sulfur dioxide is hydrated, we have found to the contrary that sulfur dioxide in essentially anhydrous media reacts rapidly and apparently quantitatively with 1-benzyl-1,4-dihydronicotinamide, an analogue of NADH, to give a yellow pyridinium salt, **1**, whose anion is one or more reduced species of sulfur dioxide. The salt obtained in liquid sulfur dioxide shows a maximum in the UV spectrum at 265 nm (95%

(1) Blankenhorn, G.; Moore, E. G. *J. Am. Chem. Soc.* **1980**, *102*, 1092.
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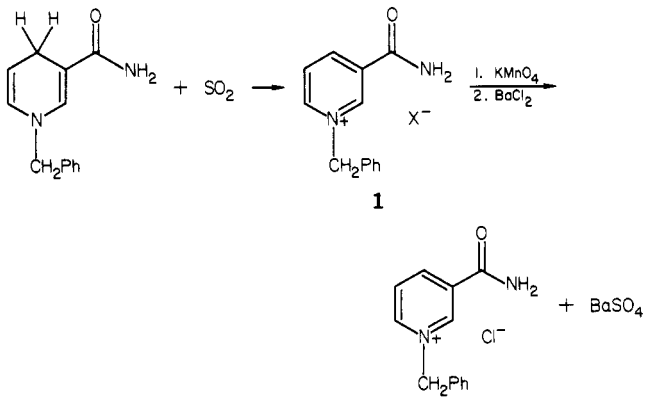
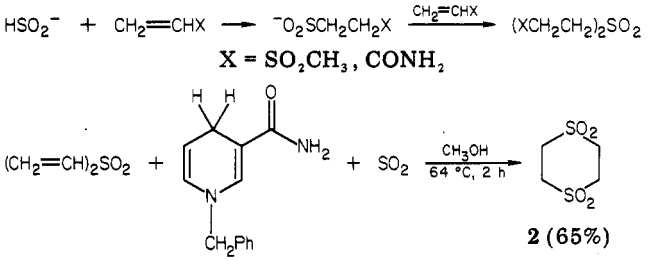


1

ethanol) characteristic of pyridinium salts.[6] The absence of absorption at 340–370 nm, even in concentrated solutions, rules out the presence of dimers that could be formed should any true pyridinyl radicals be intermediates in the reaction.[7] The anion decolorizes aqueous potassium permanganate, and treatment of the resulting solution with aqueous barium chloride gives a precipitate of barium sulfate. The pyridinium salt isolated from this reaction sequence is identified as the known 1-benzyl-3-carbamoylpyridinium chloride. Anion-exchange chromatography of the yellow salt gives 1-benzyl-3-carbamoylpyridinium chloride in 75% yield based on the dihydronicotinamide. Elemental analysis of the yellow salt indicates the anion, X^-, may be a mixture of sulfite and thiosulfate, known disproportionation products of dithionite ($S_2O_4^{2-}$).[8] The analysis also is consistent with an $S_3O_6^{2-}$ anion. Iodometric titrations[9] of this yellow salt also indicate that the anion, X^-, corresponds to a mixture of sulfite and thiosulfate ions.

In an attempt to trap an early reduced species of sulfur dioxide, we treated the dihydronicotinamide with sulfur dioxide in methanol or in *N,N*-dimethylformamide in the presence of Michael acceptors (e.g., methyl vinyl sulfone, divinyl sulfone). Sulfones were obtained from these ac-

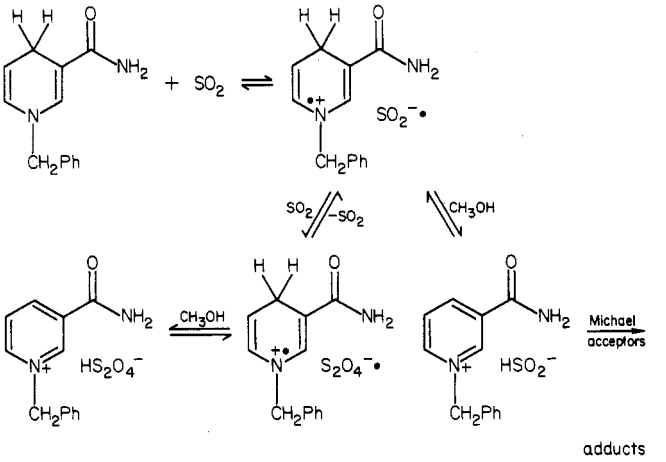


X = SO_2CH_3, $CONH_2$

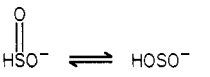
2 (65%)

ceptors in ca. 50–60% yield. Presumably, they were formed by initial addition of HSO_2^- to the Michael acceptor to give a sulfinate, which then added to a second molecule of acceptor. Divinyl sulfone gives 1,4-dithiane 1,1,4,4-tetroxide, **2**. Acrylamide gives somewhat lower yields of sulfone. No sulfone is obtained in the absence of dihydronicotinamide. Phenothiazine in small amounts is added to most reactions to retard polymerization of the vinyl compounds. A chemical reduction of sulfur dioxide by formate ion at 100 °C has been reported, and the intermediate also was trapped by Michael acceptors.[10]

Scheme I



The sulfoxylate ion, HSO_2^-, can exist in two tautomeric modifications, **3** and **4**.[1] Since the anion radical of sulfur



3 **4**

dioxide is a π radical with the electron localized mainly on the sulfur atom ($SO_2^{-\cdot}$ is isoelectronic with ClO_2),[8] the first intermediate after hydrogen atom abstraction is likely to have the structure of the first tautomer, **3**. Whether the formation of the Michael adducts requires the second tautomer, **4**, remains to be determined.

In *N,N*-dimethylformamide solvent, treatment of 1-benzyl-1,4-dihydronicotinamide with sulfur dioxide gives a green solution, λ_{max} 580 nm, which shows a broad, featureless ESR signal (g = 2.007). These observations are consistent with the presence of $S_2O_4^{-\cdot}$ ($SO_2^{-\cdot}$ + SO_2) or higher molecular weight complexes with sulfur dioxide whose spectra and ESR behavior have been reported previously from electrochemical studies on sulfur dioxide in *N,N*-dimethylformamide.[11] Previously, the sulfur dioxide radical anion has been found to react with alkyl halides to give sulfones.[12] Certain tertiary amines (e.g., triphenylamine) and secondary amines (e.g., piperidine) show ESR absorptions in liquid sulfur dioxide[13] that supports the suggestion of an initial electron-transfer step from dihydropyridine to sulfur dioxide. No evidence for a dihydropyridine radical cation has been obtained, although the broadness of the ESR spectrum may be caused by its presence. No dimers of pyridinyl radicals have been found in the reaction products. No ESR signal is observed when methanol is the solvent, and the signal observed in *N,N*-dimethylformamide is quenched on addition of methanol. In the absence of other reagents and with the exclusion of oxygen, the ESR signal slowly diminishes in intensity. The lack of an observable ESR signal in methanol may indicate that the initially formed anion radical of sulfur dioxide, $SO_2^{-\cdot}$, rapidly abstracts a hydrogen atom from the solvent, forming a cage around the radical ion pair. The radical formed from methanol then abstracts a hydrogen atom from the dihydronicotinamide, possibly via a rapid hydrogen atom transfer between neighboring methanol molecules, to give the pyridinium

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salt. Alternatively, rapid diffusion of $SO_2^{-}\cdot$ from the cage may occur followed by similar steps. The interaction of sulfur dioxide with 1-benzyl-1,4-dihydronicotinamide thus may proceed as shown in Scheme I.

These apparent one-electron transfers from a model for NADH are in accord with suggestions of Kosower[7c,14] and Bruice[15] for NAD-catalyzed enzymic reactions, which provide an alternative to the widely held view that reductions by NADH are hydride ion transfers.[16]

Registry No. 1, 16183-83-8; 1-Cl, 5096-13-9; 2, 33976-40-8; SO_2, 7446-09-5; $CH_2{=}CHSO_2CH_3$, 3680-02-2; $(CH_2{=}CH)_2SO_2$, 77-77-0; $(CH_3SO_2CH_2CH_2)_2SO_2$, 13063-95-1; $(H_2NCOCH_2CH_2)_2SO_2$, 13063-92-8; $CH_2{=}CHCONH_2$, 79-06-1; 1-benzyl-1,4-dihydronicotinamide, 952-92-1.

Supplementary Material Available: Full experimental details (6 pages). Ordering information is given on any current masthead page.

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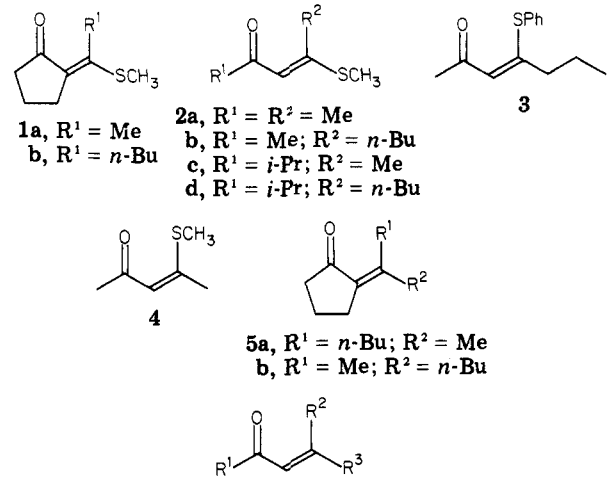
Stereoselectivity in the Addition of Organocuprates to β-Alkylthio α,β-Enones

Summary: Factors affecting the direction and degree of stereoselectivity in the conjugate addition–elimination reaction of organocuprates with β-alkylthio α,β-enones are described.

Sir: We report that the reaction of *E* β-methylthio α,β-enones with organocuprates[1] exhibits an extraordinary solvent effect and can be induced to proceed stereoselectively with either inversion or retention of configuration. While α,β-unsaturated carbonyl compounds containing good leaving groups at the β-carbon atom (e.g., halide,[2] acetate,[3] phosphate,[4] alkoxy,[5,6g] and alkylthio[6] substituents)

Chart I



readily undergo alkyl substitution upon reaction with organocuprates, the substitution has frequently occurred with predominant retention of configuration for the extensively studied ester derivatives.[2a,g,3,4,6c,6e-g] Significantly, only two reports[2a,c] have appeared that describe stereoselective substitutions for the more reactive ketone analogues that sometimes undergo nonchemoselective bis conjugate addition reactions.[6h] Our study indicates that stereoselectivity is far more difficult to obtain for ketone substrates but can be achieved by careful control of reaction conditions. These results provide an efficient and versatile synthetic route to regio- and stereospecifically substituted α,β-unsaturated ketones.[7]

β-Alkylthio α,β-enones 1 (**a**,**b**) and 2 (**a**–**d**) (Chart I) were readily prepared from the corresponding α-oxoketene dithioacetals by an established procedure.[6a,8] The phenylthio derivative 3 was obtained from 3-heptyn-2-one[9] by

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