The Reaction of Dialkylcopper Lithium Reagents with 3-Halo-2-acylaminoacrylic Acids

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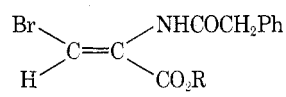
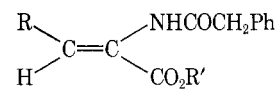
The reaction of Me_2CuLi and n-Bu_2CuLi with some 3-halo-2-acylaminoacrylic acid derivatives has been studied. Reaction of (*Z*)-3-bromo-2-(2-phenylacetamido)acrylic acid (**1**) with Me_2CuLi yielded (*Z*)-2-(2-phenylacetamido) crotonic acid (**3**), while the reaction with n-Bu_2CuLi gave a 2:1 mixture of *Z* and *E* isomers, **5** and **6**, of 2-(2-phenylacetamido)hept-2-enoic acid. In each case, the reduction product, 2-(2-phenylacetamido)acrylic acid (**4**), was formed as a minor product. The (*Z*)-3-chloroacrylate **7**, upon reaction with Me_2CuLi, gave the (*Z*)-crotonate **8**, while a 3:1 *Z* to *E* mixture of the 3-bromoacrylates **9** and **10**, yielded a product mixture of the (*Z*)- and (*E*)-crotonates **8** and **11**. These reactions thus occur by replacement of the vinylic halogen and proceed with complete or predominant retention of configuration about the double bond.

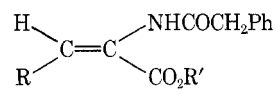
The synthetic utility of dialkylcopper lithium reagents, R_2CuLi, is well known[1] and of current interest. R_2CuLi reagents are known to undergo direct displacement of vinylic halogen by an alkyl group[2] and also to effect conjugate addition to enone systems.[3] We have studied the reaction of Me_2CuLi and n-Bu_2CuLi with 3-halo-2-acylaminoacrylic acid derivatives as a possible route for preparation of dehydroamino acids substituted in the β position with various alkyl groups and to establish the stereochemical course of the reaction. The reaction of cuprate reagents with cyclic β-halo-α,β-unsaturated ketones recently has been reported.[4]



1, R = H
2, R = Me



3, R = Me; R′ = H
4, R = H; R′ = H
5, R = n-Bu; R′ = H



6, R = n-Bu; R′ = H

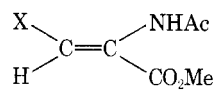
Results and Discussion

Products of the Reaction. (*Z*)-3-Bromo-2-(2-phenylacetamido)acrylic acid (**1**),[5] upon treatment with 5 equiv of ethereal Me_2CuLi in tetrahydrofuran at 0 °C, yielded a mixture for which TLC analysis revealed four components, two of which were present in minor amounts. The NMR spectrum of the mixture established the two major products to be the crotonic acid **3** of *Z* configuration and the acrylic acid **4**[6] in a 3:1 ratio. Use of only 2 equiv of Me_2CuLi furnished a more homogeneous product mixture containing only small amounts of **4**, from which **3** was obtained in 52% yield by one recrystallization from ethyl acetate.

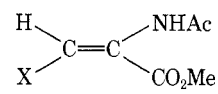
Isomerization has been reported to occur in reactions of R_2CuLi with vinyl halides[7] and α,β-acetylenic esters,[8] and likely proceeds via intermediate vinyl cuprates. To check if this were occurring, the reaction of **1** with Me_2CuLi was carried out at lower temperatures. No reaction was observed at −78 °C and it was necessary to raise the temperature to approximately −40 °C before significant reaction occurred. Then, only the *Z* isomer was observed in the NMR spectrum of the product mixture. It should be pointed out that the *Z* isomer of 2-acylaminocrotonates has been reported[9,10] to be the more stable isomer. Thus, isomerization may not be occurring in this case as the (*Z*)-3-bromoacrylates yield directly the more stable vinyl cuprate and, subsequently, crotonate of *Z* configuration.

Treatment of the 3-bromoacrylic acid **1** with an excess of n-Bu_2CuLi in tetrahydrofuran–hexane at −40 °C gave a mixture composed of six components, four of which were identified as being the heptenoic acids **5** and **6**, the acrylic acid **4**, and recovered reactant **1**. The heptenoic acids **5** and **6** typically comprised 30–60% of the product mixture and were present in an approximate ratio of 2:1, respectively. The acids **5** and **6** were each separated, though in low yield, from the product mixture by preparative TLC. The formation of the acrylic acid **4** in the above reactions, in which bromine has been replaced by hydrogen, was not unexpected as similar reduction products resulting from apparent halogen–metal exchange reactions have been reported.[2,7,11] Likewise, the nonstereospecificity as observed in reaction of **1** with n-Bu_2CuLi has been observed previously in reactions of R_2CuLi with β-halo-α,β-unsaturated sulfones[12] and β-acetoxy-α,β-unsaturated carbonyl compounds.[13]

Methyl (*Z*)-2-acetamido-3-chloroacrylate (**7**) underwent reaction with Me_2CuLi in an analogous manner as **1** to yield the (*Z*)-2-acetamidoacrylate **8**. When an approximate 3:1 isomeric mixture of the 3-bromoacrylates **9** and **10** was allowed to react with Me_2CuLi, a mixture of *Z* and *E* isomers **8** and **11** was obtained. The ratio of **8**:**11** could not readily be determined from the NMR spectrum of the mixture; however, the *Z* isomer **8** was the predominant product. The reactions of **1**, **7**, **9**, and **10** thus appear to be stereospecific with retention of configuration, a result consistent with previous studies.[2,7,14]



7, X = Cl
8, X = Me
9, X = Br



10, X = Br
11, X = Me

The possibility exists that the above 3-alkyl products are formed by a sequence of conjugate addition and elimination rather than by substitution. Casey has proposed[13] an addition–elimination sequence in the reactions of R_2CuLi with β-acetoxy-α,β-unsaturated esters. We have observed that the acrylic acid **4** did not undergo conjugate addition upon reaction with Me_2CuLi, in agreement with previous results reported[15] for α,β-ethylenic carboxylic acids. Thus, unless the 3-bromo group in **1** has an effect of enhancing conjugate addition, the above results, while not ruling out an addition–elimination process, indicate that conjugate addition may not be a significant reaction pathway in this system. Also, for-

Table I. Shift Values and Configurational Assignments for β-Haloacrylates

Registry no.	Compd	Solvent	Chemical shift, δ, of vinylic proton	Configuration
60084-43-7	9	$CDCl_3$	7.17	*Z*
		TFA	7.80	
60084-44-8	10	$CDCl_3$	7.48	*E*
		TFA	7.51	
60084-45-9	2	$CDCl_3$	7.04	*Z*
		TFA	7.77	
60084-46-0	1	TFA	7.94	*Z*
60084-47-1	7	$CDCl_3$	6.97	
		TFA	7.55	*Z*

Table II. Shift Values and Configurational Assignments for β-Alkylacrylates

			Chemical shift, δ		
Registry no.	Compd	Solvent	β-Me or -CH_2	Vinylic H	Configuration
60084-48-2	3	TFA	1.91	7.40	*Z*
60084-49-3	5	TFA	2.24	7.34	*Z*
60084-50-6	6	TFA	2.77	6.95	*E*
60027-59-0	8	$CDCl_3$	1.71	6.72	*Z*
		TFA	1.85	7.18	
60027-53-4	11	$CDCl_3$	2.02	6.90	*E*
		TFA	2.13	6.68	

mation of the acrylate **4** in these reactions is consistent with at least a portion of the reaction proceeding by a substitution process.

Stereochemistry of Reactants and Products. The stereochemistry of reactants and products involved in this study was established by use of NMR spectroscopy. Previous studies[9,16] have shown that for 2-acylaminoacrylate or crotonate derivatives, a vinylic proton cis to the acylamino group is downfield compared to a proton trans to that function. In the preparation of reactant **1**, only one geometrical isomer was obtained. Other 3-haloacrylic acids related to **1** that have been reported[5,17] also appear to be single isomers of unspecified configuration. However, Kishi and co-workers[18] recently obtained a 2:1 mixture of the *Z* and *E* isomers **9** and **10**. Following Kishi's procedure, we prepared **9** and **10** and have assigned stereochemistry to these isomers based upon the shift positions of the vinylic protons. In agreement with the previous assignment,[18] **9** is of the *Z* configuration and has the vinylic proton, being trans to the acylamino function, absorbing at higher field relative to the olefinic shift position of the *E* isomer **10** (Table I).

Reactant **1** was converted to the methyl ester **2** by methylation with dimethyl sulfate. Comparison of the NMR spectra of **2**, taken in both $CDCl_3$ and trifluoroacetic acid (TFA), with those of **9** and **10** established **2**, and consequently **1**, as being of the *Z* configuration. The *Z* isomers **2**, **7**, and **9** all showed a significant downfield shift of the vinylic proton in TFA compared to $CDCl_3$, as has been observed[9] for the *Z* isomers of crotonic acid derivatives (see Table I).

Relevant NMR data and resulting stereochemical assignments for the 3-alkylacrylates prepared in this study are given in Table II. Configuration previously has been assigned[9] to crotonates **8** and **11** in which the *Z* isomer has both the vinylic and β-methyl protons high field relative to the *E* isomer when measured in $CDCl_3$. As previously noted[9] for spectra measured in TFA as solvent, the relative positions of the β-methyl protons in the two geometrical isomers are unchanged, while the vinylic proton of the *Z* isomer is shifted downfield and the corresponding proton in the *E* isomer is shifted upfield. The net result is that the relative positions of the isomeric vinylic protons are switched in TFA relative to their positions in $CDCl_3$ and the *Z* isomer now has the low-field vinyl absorption. Since compounds **3**, **5**, and **6** were insoluble in $CDCl_3$, their spectra were measured in TFA as solvent. Comparison of the chemical shift values of **3** with **8** clearly showed **3** to have the *Z* configuration. Likewise, the relative positions of the β-methylene and vinylic protons in **5** and **6** readily allowed assignment of *Z* and *E* configuration, respectively, to these substances (see Table II).

Experimental Section

The melting points were measured on a Thomas-Hoover melting point apparatus and are uncorrected. Thin layer chromatography was done on commercially available silica gel plates with fluorescent indicator (Brinkman F-254 and 60F-254). Preparative TLC was done on 20 × 20 cm, 2-mm thick plates. The solvent systems used were A, $CHCl_3$–AcOH (95:5); B, $CHCl_3$–MeOH–AcOH (10:5:1); C, $CHCl_3$–EtOH (1:1). The compounds were located under uv irradiation and with iodine vapor. The NMR spectra were determined on a Varian Associates XL-100-12, 100 MHz, or Varian EM-360, 60 MHz, spectrophotometer, with Me_4Si as an internal reference. Solvents were removed in vacuo on a Büchi rotary evaporator. Elemental analyses were performed at M-H-W Laboratories, Garden City, Mich. Reagents used were of reagent or spectroscopic grade.

The air-sensitive alkyllithium and dialkylcopper lithium reagents were handled according to established techniques.[19] The MeLi and n-BuLi solutions were purchased from Alfa Products and were used untitrated. Both solutions were stored at room temperature and the n-BuLi solution was stored in a desiccator. Ultrapure grade cuprous iodide was purchased from Ventron, Alfa Products, and stored in a desiccator. THF was distilled from $LiAlH_4$ prior to use and stored over 5A molecular sieve.

Reaction of 1 with Me_2CuLi. To a three-neck round-bottom flask fitted with nitrogen inlet and outlet tubes and a septum capped addition funnel was added 1.68 g (8.82 mmol) of anhydrous CuI. The reaction flask was flamed out both before and after the addition of the CuI and allowed to cool under a dry, oxygen-free nitrogen flow. THF (24.5 ml) was added to the flask and the resulting slurry was stirred magnetically and cooled to 0 °C in an ice bath. A solution of MeLi (11.0 ml of 1.65 M) in ether was added dropwise over 20 min to yield a light brown solution approximately 0.25 M in Me_2CuLi. A solution of **1**[5] (0.500 g, 1.76 mmol) in 8.5 ml of THF was added over 20 min and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched by the addition of 2 ml of 3 N HCl. The mixture was allowed to warm to room temperature and was added with stirring to 125 ml of 3 N HCl, followed by extraction with 5 × 30 ml of $CHCl_3$. The combined organic extracts were filtered by suction and dried over $MgSO_4$ with simultaneous treatment with charcoal. Following filtration, the solvent was removed in vacuo to yield 0.376 g of a white solid, mp 175–177 °C dec. TLC (solvent A) showed the presence of four components, two of which seemed to be present in minor amounts. NMR analysis of the crude product mixture established that the major components were the crotonic acid **3** and the acrylic acid **4**, these being present in a ratio of 3:1, respectively. No peaks were observed that could be assigned to the other geometrical isomer of **3**. The identity of the acrylic acid **4** also was established by TLC comparison with an authentic sample[6] in three different solvent systems. The crotonic acid **3** was isolated by recrystallization from ethyl acetate; one recrystallization gave material melting at 194–195 °C dec and in a yield of 39%. This material still contained a small amount of **4** as shown by TLC analysis. An analytical sample of **3** was prepared by additional recrystallizations from ethyl acetate: mp 198–199 °C dec; TLC R_f 0.17 (A), 0.69 (B); NMR (TFA) δ 1.91 (d, 3 H, CH_3, J = 7 Hz), 4.01 (s, 2 H, CH_2Ph), 7.40 (q, 1 H, vinyl, J = 7 Hz) overlapped with 7.46 (s, 5 H, Ph), 7.84 (s, 1 H, NH).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.44; H, 6.13; N, 6.17.

Reaction of **1** with 2 equiv of Me_2CuLi as used above resulted in negligible formation of **4**; one recrystallization of the product mixture from ethyl acetate gave crotonic acid **3** in 52% yield.

Treatment of **1** as above, except that the reaction was run at −78 °C for 2 h in a dry ice–acetone bath, gave upon workup mainly recovered reactant **1** as shown by TLC and NMR analysis. When the reaction was carried out at −40 to −50 °C and for reaction periods of 45–90 min, the product mixture was composed of reactant **1** and the

Z isomer **3**. None of the *E* isomer was detected in the NMR spectrum of the product mixture.

Reaction of 1 with *n*-Bu_2CuLi. Anhydrous CuI (1.68 g, 8.82 mmol), treated as above, was suspended in 27 ml of anhydrous THF and cooled to −40 °C in a dry ice–2-propanol bath. A solution of *n*-BuLi (8.5 ml of 2.1 M) in hexane was added dropwise over a 20-min period to produce a dark brown solution approximately 0.25 M in *n*-Bu_2CuLi. A solution of **1** (0.500 g, 1.76 mmol) in 10 ml of THF was added dropwise over 20 min, following which the reaction was allowed to proceed for an additional 1 h and then quenched at −40 °C by dropwise addition of 2.5 ml of 3 N HCl over an 8-min period. The mixture was stirred for 10 min at −40 °C, after which the cooling bath was removed and the mixture allowed to warm to room temperature. The reaction mixture was poured with stirring into 120 ml of 3 N HCl and the resulting mixture was filtered by suction through a pad of Celite. The filtrate was extracted with 5 × 30 ml of $CHCl_3$ and the combined organic extracts were simultaneously treated with charcoal and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo to give 0.414 g of a yellow solid, mp 140–155 °C dec. TLC (solvent A) showed the presence of six components, two of which were identified as being **1** and **4** by TLC comparison with authentic samples. NMR analysis of the mixture showed it to consist of the heptenoic acids **5** and **6**, the acrylic acid **4**, the reactant **1**, plus unidentified components. The ratio of **5**:**6**, as measured from the NMR spectrum of the product mixture, varied in different runs from approximately 2:1 to 3.6:1, with the total combined yield of **5** and **6** varying from 30–60%. Compounds **5** and **6** were separated by preparative TLC using solvent A. Each 2-mm silica gel plate was treated by application of 150 mg of sample in 1.5 ml of THF followed by multiple developments to effect separation. The appropriate bands were removed from each plate and extracted with three portions of MeOH. The extracts were filtered several times utilizing Celite to remove traces of silica gel and the solvent was removed in vacuo.

The lower band material proved to be the *Z* isomer and was obtained as a light yellow oil in 11% yield from **1**, which after dissolution in $CHCl_3$, filtration, and evaporation of the filtrate in vacuo yielded a glassy solid. Trituration of this solid with ether followed by two recrystallizations from 2-propanol gave a white solid, mp 205–206 °C dec. TLC and NMR analysis indicated this material to be homogeneous; however, two attempts to obtain satisfactory analytical data were unsuccessful, each analysis varying from the other. TLC R_f 0.18 (A), 0.35 (C); NMR (TFA) δ 0.95 (m, 3 H, CH_3), 1.45 (m, 4 H, $-CH_2CH_2-$), 2.24 (q, 2 H, $-CH_2C=$, J = 7 Hz), 4.00 (s, 2 H, $-COCH_2-$), 7.34 (t, 1 H, vinyl, J = 7 Hz) overlapped with 7.46 (s, 5 H, Ph), 7.78 (s, 1 H, NH).

The *E* isomer was isolated from an upper band of the preparative plate as a light yellow solid, mp 155–158.5 °C, 14% yield from **1**. This material was recrystallized twice from water and dried in a vacuum desiccator over P_2O_5 to give a white solid: mp 164–165 °C dec; R_f 0.36 (A), 0.50 (C); NMR (TFA) δ 1.0 (m, 3 H, CH_3), 1.5 (m, 4 H, $-CH_2CH_2-$), 2.77 (q, 2 H, $-CH_2C=$, J = 7 Hz), 3.98 (s, 2 H, $-COCH_2$), 6.95 (t, 1 H, vinyl, J = 7 Hz), 7.43 (m, 5 H, Ph), 8.06 (s, 1 H, NH).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.13; H, 7.20; N, 5.28.

Methyl 3-Bromo-2-(2-phenylacetamido)acrylate (2). Following the basic methylation procedure of Rothstein,[20] a mixture of **1** (1.00 g, 3.52 mmol), Na_2CO_3 (0.219 g, 2.07 mmol), NaOMe (0.223 g, 4.13 mmol), and Me_2SO_4 (0.67 g, 5.31 mmol) in 10 ml of anhydrous MeOH was heated at reflux for 1.75 h. After cooling to room temperature, 4 ml of water was added, the mixture was stirred for 30 min and filtered by suction, and the solvent was removed in vacuo. The residue was extracted with three portions of $CHCl_3$ and the combined extract was dried over $MgSO_4$. Filtration and removal of the solvent in vacuo gave 0.686 g (65%) of a pale yellow solid, mp 96–97.5 °C. Recrystallization from ether furnished product melting at 97.5–98 °C (lit.[5] 100–101 °C, prepared by esterification of **1** with diazomethane): R_f 0.40 (A); NMR ($CDCl_3$) δ 3.71 (s, 2 H, $-CH_2Ph$), 3.78 (s, 3 H, OCH_3), 6.92 (s, 1 H, NH), 7.04 (s, 1 H, vinyl), 7.36 (s, 5 H, Ph); NMR (TFA) δ 3.98 (s, 2 H, $-CH_2Ph$), 4.00 (s, 3 H, OCH_3), 7.45 (s, 5 H, Ph), 7.74 (s, 1 H, NH), 7.77 (s, 1 H, vinyl).

Methyl 3-Chloro-2-acetamidoacrylate (7). In 500 ml of dry CCl_4 (stored over Linde 3A molecular sieves) was dissolved 28.6 g (20 mmol) of methyl 2-acetamidoacrylate.[21] Chlorine gas was passed into the stirred solution at room temperature until a permanent yellow color developed, then the yellow solution was stirred for 10 min at room temperature. The solvent was removed in vacuo to yield a colorless oil. The oil was dissolved in 500 ml of dry CH_3CN (stored over Linde 3A) and 23.2 g (20.7 mmol) of 1,4-diazabicyclo[2.2.2]octane was added to the solution. The reaction mixture was stoppered and stirred for 1 h at room temperature. The precipitated hydrochloride salt was filtered and the solvent removed in vacuo to yield a brown precipitate. The precipitate was extracted three times with 100 ml of cold EtOAc and the combined extract filtered through Celite. The EtOAc was removed in vacuo to yield a brown oil which solidified upon standing overnight. The brown solid was recrystallized from Et_2O to yield a white solid. Additional crops were obtained after treatment of the Et_2O solution with Norit at room temperature. Recrystallization of the combined crops from Et_2O afforded **7** in 41% yield (14.6 g): mp 96–97 °C; NMR ($CDCl_3$) δ 2.13 (s, 3 H, Ac), 3.83 (s, 3 H, Me ester), 7.00 (s, 1 H, vinylic), and a broad band centered at 7.50 (1 H, NH).

Anal. Calcd for $C_6H_8ClNO_3$: C, 40.58; H, 4.54; N, 7.89. Found: C, 40.64; H, 4.60; N, 7.88.

Reaction of β-Chloroacrylate 7 with Me_2CuLi. A solution of **7** (0.30 g, 1.69 mmol) in 5.2 ml of THF was added dropwise over a period of 10 min to 2 equiv of Me_2CuLi, prepared as described above from 0.64 g (3.36 mmol) of CuI and 4.1 ml (6.72 mmol) of 1.65 M ethereal MeLi, in 15 ml of THF at 0 °C. The reaction was allowed to proceed for 2 h at 0 °C and then the mixture was worked up as above except that the acidic aqueous phase was saturated with NaCl prior to extraction with $CHCl_3$. A light yellow oil (0.26 g) was obtained, the NMR spectrum of which, upon comparison with reported spectral data,[9,10] showed this material to be the *Z* isomer **8**.

Preparation of (*Z*)- and (*E*)-2-Acetamido-3-bromoacrylic Acid Methyl Esters (9 and 10). Following the method of Kishi,[18] methyl 2-acetamidoacrylate[20] (0.50 g, 3.49 mmol) in 20 ml of CH_2Cl_2 was treated dropwise with a solution of bromine in CH_2Cl_2 until a permanent color persisted. After stirring at room temperature for 10 min, 0.39 g (3.48 mmol) of 1,4-diazabicyclo[2.2.2]octane was added and the reaction mixture was stirred for an additional 40 min. The precipitate was filtered through Celite and the solvent removed in vacuo to yield an oil. The oil was dissolved in 75 ml of anhydrous Et_2O, the resulting precipitate was removed by filtration, and the solvent was removed in vacuo to yield 0.58 g of an oil. The NMR spectrum of this oil was consistent for a mixture of **9** and **10** in an approximate ratio of 3:1, plus other unidentified components. Preparative TLC using $CHCl_3$–AcOH (95:5) as elutant effected separation of **9** and **10** for which the first and second bands above the origin corresponded to **9** and **10**, respectively: NMR ($CDCl_3$) (*Z* isomer) δ 2.13 (s, 3 H, acetyl), 3.80 (s, 3 H, methyl ester), 7.10 (s superimposed on broad peak, 2 H, vinylic and amide protons); (*E* isomer) δ 2.13 (s, 3 H, acetyl), 3.92 (s, 3 H, methyl ester), 7.78 (broad s, 1 H, NH), 8.00 (s, 1 H, vinylic proton). We have observed that the shift positions of the vinylic protons for mixtures of **9** and **10** were not reproducible among various samples; however, the relative positions of the vinylic protons for the two isomers did not change.

Reaction of a Mixture of 9 and 10 with Me_2CuLi. A 3:1 mixture of **9** and **10** (0.57 g, 2.57 mmol) was treated with 2 equiv of Me_2CuLi in THF as described above for **7**. An NMR spectrum of the crude reaction product showed both crotonates **8** and **11** to be present; a determination of the relative amounts of these isomers was not practical owing to the lack of separation between isomeric peaks and to overlap with absorption caused by impurities present in the sample.

Attempted Conjugate Addition of Me_2CuLi to Acrylic Acid 4. The acrylic acid **4** (0.500 g, 2.44 mmol) was treated with an excess of Me_2CuLi in the same manner as described above for the reaction of Me_2CuLi with the 3-bromoacrylic acid **1**. Following workup, TLC and NMR analysis on the crude reaction mixture established that the reactant **4** was the major component with two other minor components being present. The NMR spectrum did not show any peaks assignable to an ethyl group, as would be expected for any products formed by conjugate addition.

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Registry No.—**7** HCl, 60084-51-7; Me_2CuLi, 15681-48-8; *n*-Bu_2CuLi, 24406-16-4; methyl 2-acetamidoacrylate, 35356-70-8.

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Solvents for Aromatic SRN1 Reactions[1a]

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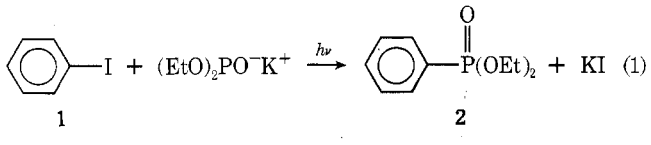
Whereas previously aromatic SRN1 reactions were conducted almost exclusively in ammonia, it is now found that dimethyl sulfoxide is a good solvent for photostimulated reactions of diethyl phosphite ion, thiophenoxide ion, and acetone enolate ion with iodobenzene. Yields in the iodobenzene–diethyl phosphite ion reaction were also high in acetonitrile and dimethylformamide and fairly good in *tert*-butyl alcohol, but poor in hexamethylphosphoric triamide and some other common dipolar, aprotic solvents. In *tert*-butylamine, attempted reactions with thiophenoxide and acetone enolate ions were not very satisfactory, but iodobenzene as well as *m*-bromoiodobenzene underwent rapid photostimulated reaction with diethyl phosphite ion. In water, poor yields were obtained in photostimulated reactions of thiophenoxide ion with two substrates which were the more reactive of several tried.

The SRN1 mechanism of aromatic substitution, first recognized in 1970,[2] involves radical and radical anion intermediates and electron transfer steps but the overall consequence is that of nucleophilic substitution. A representative reaction is that of iodobenzene with potassium diethyl phosphite (eq 1).[3]



1 2 (1)

Other nucleophiles successfully involved in aromatic SRN1 reactions include arenethiolate ions,[4] the amide ion,[2,5] ketone enolate ions,[6-10] α-cyanoalkyl carbanions,[2,11] picolyl anions,[12] and several carbanions of other sorts.[8] The mechanism tolerates substituents such as alkyl, alkoxy, and carboxylate ($-COO^-$) groups and is remarkably insensitive to the steric effects of groups ortho to the site of substitution. These reactions usually require stimulation, for purposes of chain initiation, by photons or electrons.

The SRN1 mechanism of substitution was initially discerned for certain reactions at aliphatic sites by Kornblum[13] and Russell[14] and their associates and has recently been reviewed as a mechanism of substitution at saturated carbon by Kornblum.[15] As a radical chain mechanism, it involves initiation, propagation, and termination steps but, since the initiation and termination steps are not very well understood and probably vary in character from case to case, we sketch in Scheme I only the probable cycle of propagation steps. In Scheme I, ArX is a generalized aromatic substrate and Y^- a generalized nucleophile.

Liquid ammonia has been the solvent for nearly all the aromatic SRN1 reactions reported from this laboratory. Bunnett and Sundberg[9] did report a few experiments on the use of other solvents for the reaction of bromobenzene with potassium acetone enolate. The investigations of Kornblum and Russell and their co-workers were conducted mainly in dipolar aprotic solvents such as dimethylformamide (DMF), dimethyl sulfoxide (Me_2SO), and hexamethylphosphoric triamide (HMPT). In order to assess the utility of diverse solvents for aromatic SRN1 reactions, we carried out the studies now described.

Scheme I

$$[ArX]\cdot^- \rightarrow Ar\cdot + X^- \quad (2)$$

$$Ar\cdot + Y^- \rightarrow [ArY]\cdot^- \quad (3)$$

$$[ArY]\cdot^- + ArX \rightarrow [ArX]\cdot^- + ArY \quad (4)$$

General Considerations. An obvious requirement is that a solvent should dissolve the reactants, usually a nonpolar organic compound and an alkali metal salt of an anionic nucleophile. Another, for photostimulated reactions, is that the solvent be transparent to the light which provokes reaction, which is probably about 300–380 nm.

Most of the nucleophiles that have been successfully involved in aromatic SRN1 reactions are highly basic. The acidity of the solvent must be low enough so that it does not protonate the nucleophile very much under the reaction conditions. Also, a rather acidic solvent might protonate one of the radical anion intermediates, especially $[ArY]\cdot^-$, in the manner of the Birch reduction.[16] Inasmuch as electron transfer steps are involved, solvents which accept electrons readily (e.g., nitrobenzene) or irreversibly (CCl_4) are unlikely to be satisfactory.

Solvents with which aryl radicals can readily react, especially to abstract hydrogen atoms, present a problem inasmuch as the by-product radicals from hydrogen atom abstraction