C-5 Functionalization of Trisubstituted Imidazoles with Azodicarbonyl Compounds

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Received June 30, 1995

Certain 1,2,4-trisubstituted imidazoles underwent electrophilic attack of azodicarbonyl compounds on the 5-position to form 5-(1,2-dialkoxycarbonyl)hydrazino- and 5-(4-phenyl-3,5-dioxo-1,2,4-triazolidin-1-yl)imidazole derivatives in moderate to high yields. The reaction was highly susceptible to the nature and the substitution pattern of the substituents on the imidazole ring. Thus 1,4-di- or 1,2,5-trisubstitued imidazoles, and 2-methylsulfinylimidazoles gave no reaction. Reductive cleavage of the tetrasubstituted imidazoles with zinc dust-acid gave the 1- or 1,2-cleaved product depending upon the reaction temperature, but the hydrazino moiety remained intact.

J. Heterocyclic Chem., **33**, 41 (1996).

In a previous paper [1], we described the [4 + 2] cycloaddition of the specifically structured imidazole derivatives with electron-deficient acetylenes. The reaction led directly to the formation of the retro-Diels-Alder products, pyrroledicarboxylates, but the Diels-Alder adducts have not been isolated. In contrast to the behavior of acetylenic dienophiles, ethylenic ones have been known to give isolable adducts [2] and stable adducts were reported to be obtained from the reaction between oxazoles and diethyl azodicarboxylate [3]. It has recently been reported, however, that a vinylimidazole derivative did not give any [4 + 2] cycloadducts with diethyl azodicarboxylate but rather an azetidine derivative formed by the reaction involving the side chain [4].

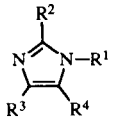
We have preliminarily attempted to react 1-benzylideneamino-2-methylthio-4-phenyl-1*H*-imidazole (**5**), one of the imidazoles which gave the retro-Diels-Alder products upon reaction with dimethyl acetylenedicarboxylate, with dimethyl azodicarboxylate (DMAZD) in order to isolate the cycloadduct and found that DMAZD behaved as an electrophile rather than as a dienophile giving 1-benzylideneamino-5-(1,2-dimethoxycarbonyl)-hydrazino-2-methylthio-4-phenyl-1*H*-imidazole (**17**) in high yield. To the best of our knowledge, the reaction between imidazoles and azodicarbonyl compounds has not afforded any products involving the ring carbon of imidazole.

The present paper describes the electrophilic substitution of 1,2,4-trisubstituted imidazole derivatives with azodicarbonyl compounds and the chemical modifications of the substituted products.

In general, the reaction of 1,2,4-trisubstituted imidazoles **1-8** with DMAZD was performed by heating an equimolar mixture of the starting materials in chlorobenzene at 100-110° for 2 hours. Removal of the solvent under reduced pressure followed by crystallization of the residue from an appropriate solvent gave the 5-hydrazinoimidazoles **13-19** in 63-90% yields. Imidazoles **6** and **7** required a longer reaction time than the typical conditions in order to achieve satisfactory yields. Crystallization of the crude compound **16** was unsuccessful from any solvents; it could be purified by chromatography on silica gel followed by recrystallization from diisopropyl ether. Hindered azodicarboxylates, such as azodiisopropyl esters, could also give rise to the Michael addition product **20** with imidazole **5** in good yield [5].

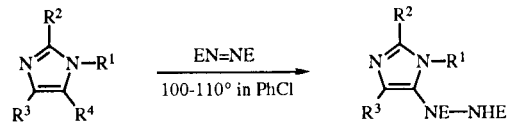
Table 1

Imidazole Derivatives Used for the Reaction with Azodicarbonyl Compounds



Compound No.	R^1	R^2	R^3	R^4
1	NH_2	SCH_3	C_6H_5	H
2	CH_3CONH	SCH_3	C_6H_5	H
3	$CH_3CH{=}N$	SCH_3	C_6H_5	H
4	$C_6H_5CH{=}N$	SCH_3	CH_3	H
5	$C_6H_5CH{=}N$	SCH_3	C_6H_5	H
6	$C_6H_5CH{=}N$	SCH_3	$4\text{-}CH_3OC_6H_4$	H
7	$C_6H_5CH{=}N$	SCH_3	$4\text{-}O_2NC_6H_4$	H
8	$C_6H_5CH{=}N$	SCH_3	C_6H_5	D
9	$C_6H_5CH{=}N$	SCH_3	H	C_6H_5
10	$CH_3CH{=}N$	$SOCH_3$	C_6H_5	H
11	$C_6H_5CH{=}N$	$SOCH_3$	C_6H_5	H
12	CH_3CO	H	C_6H_5	H

Scheme 1



1-8

E

13-19 CO_2CH_3
20 $CO_2CH(CH_3)_2$
21, 22 $OCN(C_6H_5)CO$

Table 2

Analytical and Physical Data for 5-(1,2-Dimethoxycarbonyl)hydrazinoimidazoles

Compound No.	Yield (%)	Mp°C (Solvent)	Formula (Molecular Weight)	Analysis (%) Calcd/Found			M+ (Relative Intensity)
13	69	181-182 (EtOH)	$C_{14}H_{17}N_5O_4S$ (351.3)	47.86	4.88	19.94	
				47.79	4.94	19.57	351 (97)
14	75	185-186 (EtOH)	$C_{16}H_{19}N_5O_5S$ (393.4)	48.85	4.87	17.81	
				48.55	4.81	17.74	393 (100)
15	81	148-149 (EtOH)	$C_{16}H_{19}N_5O_4S$ (377.4)	50.92	5.08	18.56	
				50.77	5.03	18.33	377 (100)
16	90	147-150 (*i*-Pr_2O)	$C_{16}H_{19}N_5O_4S$ (377.4)	50.92	5.08	18.56	
				50.96	5.14	18.35	377 (100)
18	63	146-148 (*i*-PrOH)	$C_{22}H_{23}N_5O_5S$ (469.4)	56.28	4.94	14.92	
				56.31	4.89	14.82	469 (100)
19	79	206 (C_6H_6)	$C_{21}H_{20}N_6O_6S$ (484.4)	52.06	4.16	17.35	
				51.93	4.22	17.25	484 (100)

Another azodicarbonyl compound, 4-phenyl-1,2,4-triazolin-3,5-dione (PTAD), in spite of its high reactivity [6], gave the corresponding addition products with imidazole **1** or **5** in less acceptable yields. Imidazoles **9-12** gave no reaction with DMAZD under standard reaction conditions, resulting in the total recovery of the starting materials. The unreactivity of these imidazoles toward the electrophilic DMAZD might be ascribed to the lack of the activating effect of the methylthio group (for **9**) or electron-withdrawal by the methylsulfinyl group (for **10** and **11**) or both (for **12**).

Table 3

Spectral Data for 5-(1,2-Dimethoxycarbonyl)hydrazinoimidazoles

Compound No.	UV λmax (nm) (log ε) [a]	IR ν (cm^{-1}) [b]
13	203 (4.36), 219 (4.25), 264 (4.09)	3416, 3350, 1745
14	203 (4.38), 218 (4.24), 261 (4.16)	3400, 3300, 1757, 1737
15	204 (4.35), 218 (4.24), 259 (4.13)	3403, 1770, 1750
16	205 (4.37), 254 (4.24)	3414, 3300, 1766, 1747
18	205 (4.55), 267 (4.50), 339 (3.79)	3398, 1769, 1749
19	205 (4.47), 252 (4.29), 289 (4.17), 359 (4.21)	3400, 1769, 1754

[a] In ethanol. [b] In carbon tetrachloride.

Chemical modifications of 5-hydrazinoimidazole **17** through reductive cleavage by zinc/acetic acid gave **23** at room temperature or **24** at elevated temperatures. Under the conditions of acid hydrolysis, imidazole **17** gave aminoimidazole derivative **13**.

The structures of the new imidazole derivatives **13-24** were confirmed by spectral data and the chemical behavior of 5-deuteriated imidazole. Thus, when 1-benzylideneamino-5-deuterio-2-methylthio-4-phenyl-1*H*-imidazole (**8**) [7] was subjected to similar reaction conditions with DMAZD, the product was identical with that formed from imidazole **5**. As a result of the reaction, the deuterium at the 5-position of **8** appeared on the nitrogen of the hydrazino moiety and thus was converted into an exchangeable deuterium atom. It should be exchanged with a proton during work up to produce **17**, indicating explicitly the reactive site of the starting imidazole. Further support comes from the carbon-13 nmr data as to the substitution reaction on the ring carbon of imidazole. The starting imidazoles, *e.g.*, **3-6**, had the C-5 resonances at δ 105.1-107.4 ppm as doublets ($^1J_{CH}$ 190-191 Hz), after the reaction, however, large downfield shifts were observed (17.3-18.6 ppm) with the concomitant change into singlets (Table 5). The ultraviolet (uv) spectral data provide other support for the structure of the hydrazinoimidazoles. Thus starting imidazole **5** had three maximum absorption bands at 206 (log ε 4.42), 277 (4.44) and 343 (3.98) nm, while the corresponding

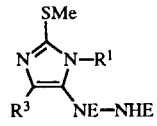
Table 4

^{1}H NMR Data for 5-(1,2-Dimethoxycarbonyl)hydrazinoimidazoles

Compound No.	^{1}H NMR (deuteriochloroform) δ, J (Hz)
13	2.66 (s, 3H, SCH_3), 3.71 and 3.87 (each s, 3H, OCH_3), 5.22 (broad s, 2H, NH_2), 7.30-7.70 (m, 6H, Ar-H and NH)
14	2.17 (s, 3H, $COCH_3$), 2.67 (s, 3H, SCH_3), 3.74 (s, 6H, 2 x OCH_3), 7.27-7.68 (m, 6H, Ar-H and NH), 9.74 (broad s, 1H, NH)
15	2.24 (d, 3H, J = 5.4 Hz, $CHCH_3$), 2.69 (s, 3H, SCH_3), 3.67 and 3.78 (each s, 3H, 2 x OCH_3), 7.04 (broad s, 1H, NH), 7.28-7.85 (m, 5H, Ar-H), 8.13 (q, 1H, J = 4.8 Hz, $CHCH_3$)
16	2.22 (s, 3H, 4-CH_3), 2.59 (s, 3H, SCH_3), 3.69 and 3.72 (each s, 3H, 2 x OCH_3), 7.20 (s, 1H, NH), 7.30-7.84 (m, 5H, Ar-H), 8.55 (s, 1H, N=CH)
18	2.72 (s, 3H, SCH_3), 3.64, 3.76 and 3.82 (each s, 3H, 3 x OCH_3), 6.95 and 7.82 (each d, 2H, J = 8.0 Hz, Ar-H), 7.16 (broad s, 1H, NH), 7.46-7.54 (m, 5H, Ar-H), 8.79 (s, 1H, N=CH)
19	2.68 (s, 3H, SCH_3), 3.58 and 3.69 (each s, 3H, 2 x OCH_3), 7.35-7.88 (m, 6H, Ar-H and NH), 8.18 (s, 4H, Ar-H), 8.62 (s, 1H, N=CH)

Table 5

Chemical Shift Values of Imidazole Ring Carbons [a]

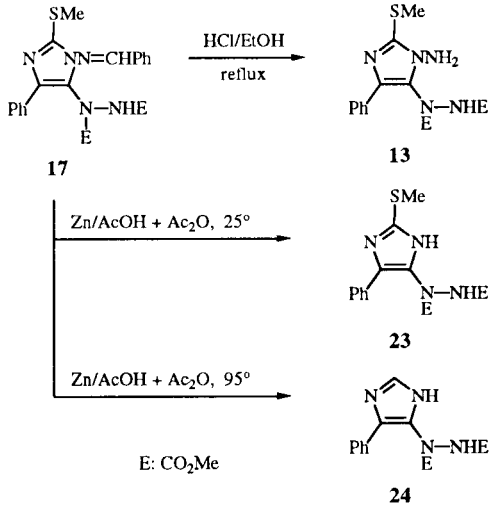


No.	R^1	R^3	E	C-2	C-4	C-5
13	NH_2	Ph	CO_2Me	144.3	133.8	126.5
14	NHAc	Ph	CO_2Me	144.5	134.3	124.4
15	N=CHMe	Ph	CO_2Me	138.6	134.4	123.9
16	N=CHPh	Me	CO_2Me	138.1	133.9	124.9
17	N=CHPh	Ph	CO_2Me	139.5	134.7	124.6
18	N=CHPh	p-$MeOC_6H_4$	CO_2Me	139.3	134.8	123.8
19	N=CHPh	p-$O_2NC_6H_4$	CO_2Me	139.7	138.7	126.4
20	N=CHPh	Ph	CO_2i-Pr	140.1	134.7	124.8
21	NH_2	Ph	O=CN(Ph)C=O	144.6	135.6	121.2
22	N=CHPh	Ph	O=CN(Ph)C=O	141.0	137.7	118.6
23	H	Ph	CO_2Me	139.1	135.0	124.8

[a] δ, ppm in deuteriochloroform.

hydrazinoimidazole **17** showed substantially the same bands at 207 (4.45), 266 (4.42) and 330 (3.72) nm. The characteristic bands at the longest wavelength have been found to occur only when the three aromatic rings of 1,2,4-trisubstituted imidazoles lay in coplanar conformations and thus conjugated [8]. Consequently the electrophilic substitution of 1,2,4-trisubstituted imidazoles by DMAZD resulted in the introduction of the 1,2-dimethoxycarbonylhydrazino group into position **5**. In view of the decrease in intensity and the hypsochromic shift of the 330-nm band of **17**, the substitution adjacent to the phenyl group might somewhat disturb the coplanarity of the aromatic rings.

Scheme 2



EXPERIMENTAL

Melting points are uncorrected. Microanalyses were performed with a Yanaco CHN CORDER MT-5 analyser at the Microanalytical Laboratory of Kitasato University. The ir, uv and mass spectra were recorded on a Perkin-Elmer 983, JASCO UVIDEC 610 and JMS-AX 505 HA instruments, respectively. The ^1H and ^{13}C nmr spectra were obtained with a JNM EX-400 (400 MHz) or a JNM FX-90Q (90 MHz) spectrometer. Preparative high-performance liquid chromatography (hplc) was carried out on a Kusano Kagaku KHLC-201 instrument with a 300 x 22 or 300 x 15 mm glass column packed with silica gel.

Preparation of New Imidazoles **10** and **11**.

1-Ethylideneamino-2-methylsulfinyl-4-phenyl-1*H*-imidazole (**10**).

A mixture of 1-ethylideneamino-2-methylthio-4-phenyl-1*H*-imidazole (**3**) (0.23 g, 1 mmole), 30% aqueous hydrogen peroxide (0.1 ml, *ca.* 1 mmole) and acetic acid (1 ml) was stirred at room temperature for 4 hours and then evaporated under reduced pressure. The solid residue was recrystallized from acetone to give analytically pure **10** as fine prisms (0.12 g, 49%), mp 174-175°; ir (chloroform): ν 1050 vs (S=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.27 (d, 3H, J = 5.4 Hz, CMe), 3.20 (s, 3H, SOMe), 7.33-7.82 (m, 5H, aromatic), 7.66 (s, 1H, H-5) and 8.03 (q, 1H, J = 5.7 Hz, N=CH); ms: (relative intensity): 247 (M^+, 100), 232 (45) and 200 (47).

Anal. Calcd. for $C_{12}H_{13}N_3OS$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.08; H, 5.26; N, 17.12.

1-Benzylideneamino-2-methylsulfinyl-4-phenyl-1*H*-imidazole **11**.

This compound was similarly obtained as fiber-like crystals, mp 192-193° (from acetone); ir (chloroform): ν 1047 s (S=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.20 (s, 3H, SOMe), 7.28-7.86 (m, 10H, aromatic), 7.88 (s, 1H, H-5) and 8.47 (s, 1H, N=CH); ms: m/z (relative intensity): 309 (M^+, 81) and 191 (100).

Anal. Calcd. for $C_{17}H_{15}N_3OS$: C, 66.01; H, 4.89; N, 13.59. Found: C, 65.99; H, 4.92; N, 13.63.

Reaction of 1-Benzylideneamino-2-methylthio-4-phenyl-1*H*-imidazole (**5**) with DMAZD. A Typical Procedure for Functionalization of the Imidazole Ring.

Imidazole **5** (2.93 g, 10 mmoles) and DMAZD (1.46 g, 10 mmoles) were dissolved in chlorobenzene (50 ml) and the solution was heated at 100-110° (bath temperature) for 2 hours. After removal of the solvent under reduced pressure, the residue was crystallized from ethanol to give compound **17** as a yellow crystalline powders (3.90 g, 89%). A one-gram portion of the product was recrystallized from ethanol to afford pure **17** as yellow prisms, mp 137-138°; ir (carbon tetrachloride): ν 3397 (NH), 1769 and 1750 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.73 (s, 3H, CH_3), 3.58 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 7.06 (s, 1H, NH, exchangeable), 7.10-7.98 (m, 10H, aromatic), 8.81 (s, 1H, N=CH); ms: m/z (relative intensity): 439 (M^+, 100), 365 (40), 230 (33).

Anal. Calcd. for $C_{21}H_{21}N_5O_4S$: C, 57.40; H, 4.82; N, 15.94. Found: C, 57.42; H, 4.89; N, 15.85.

Reaction of 1-Benzylideneamino-2-methylthio-4-phenyl-1*H*-imidazole (**5**) with Diisopropyl Azodicarboxylate.

A mixture of imidazole **5** (0.29 g, 1 mmole) and diisopropyl azodicarboxylate (0.20 g, 1 mmole) in chlorobenzene (5 ml) was heated at 100-110° (bath temperature) for 2 hours and evaporated under reduced pressure. The remaining amorphous solid was subjected to column chromatography on silica gel (Wakogel C-300, 35 g), using a benzene-ethanol mixture (99:1 by volume) as the eluent to collect a homogeneous fraction, from which the desired product (0.37 g, 89%) [5] was obtained. Recrystallization from methanol gave compound **20** as pale yellow prisms, mp 135.5-136.5°; uv (ethanol): λmax 204 (log ε = 4.50), 268 (4.45), 342 (3.83) nm; ir (carbon tetrachloride): ν 3395 (NH), 1730 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10-1.60 [m, 12H, 2 x $CH(CH_3)_2$], 2.73 (s, 3H, SCH_3), 4.94 [m, 2H, 2 x $CH(CH_3)_2$], 6.87 (s, 1H, NH), 7.33-7.95 (m, 10H, aromatic), 8.93 (s, 1H, N=CH); ms: m/z (relative intensity) 495 (M^+, 83), 408 (100), 322 (42), 217 (67), 104 (73).

Anal. Calcd. for $C_{25}H_{29}N_5O_4S$: C, 60.59; H, 5.90; N, 14.13. Found: C, 60.71; H, 5.96; N, 14.01.

1-Amino-2-methylthio-4-phenyl-5-(4-phenyl-3,5-dioxo-1,2,4-triazolidin-1-yl)-^1H-imidazole (**21**).

This compound was obtained according to the method for preparing compound **17** starting with imidazole **1** and PTAD as a crystalline powder (from ethanol), yield 35%, mp 202.5-204° dec; uv (ethanol): λmax 202 (log ε = 4.63), 218 (4.47), 258 (4.20); ir (chloroform): ν 3362 (NH), 1731, 1788 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.62 (s, 3H, SCH_3), 5.90 (s, 2H, NH_2), 7.29-7.81 (m, 10H, aromatic), 11.36 (bs, 1H, NH); ms: m/z (relative intensity) 380 (M^+, 23), 231 (20), 119 (100).

Anal. Calcd. for $C_{18}H_{16}N_6O_2S$: C, 56.84; H, 4.24; N, 22.10. Found: C, 56.69; H, 4.40; N, 21.78.

1-Benzylideneamino-2-methylthio-4-phenyl-5-(4-phenyl-3,5-dioxo-1,2,4-triazolidin-1-yl)-1*H*-imidazole (**22**).

This compound was obtained by the same method as for the preparation of **21** starting with imidazole **5** and PTAD as granular crystals (from ethanol), yield 31%, mp 203-205° dec; uv (ethanol): λmax 203 (log ε = 4.62), 266 (4.32), 336 (3.80) nm; ir (chloroform): ν 3353 (NH), 1731 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.77 (s, 3H, SCH_3), 7.32-7.85 (m, 10H, aromatic), 7.42 (s, 1H, NH), 7.45 (s, 5H, aromatic), 8.41 (s, 1H, N=CH); ms: m/z (relative intensity) 468 (M^+, 70), 293 (32), 245 (77), 104 (93), 77 (100).

Anal. Calcd. for $C_{25}H_{20}N_6O_2S$: C, 64.09; H, 4.30; N, 17.94. Found: C, 64.04; H, 4.43; N, 18.01.

5-(1,2-Dimethoxycarbonyl)hydrazino-2-methylthio-4-phenyl-1*H*-imidazole (**23**). Reductive Cleavage of Compound **17**.

A mixture of imidazole **17** (1.0 g, 2.3 mmoles), zinc powder (20.0 g), acetic anhydride (31.5 ml) in acetic acid (63.0 ml) was stirred at room temperature for 3 hours and then filtered to remove the excess zinc and any insoluble material. The filtrate was evaporated under reduced pressure and the residue taken up in chloroform (50 ml). After washing with 10% aqueous sodium carbonate and evaporation, the residue (0.9 g) was subjected to column chromatography on silica gel (Wakogel C-300, 60 g) using a chloroform-methanol mixture (99:1 by volume) as an eluent. Fractions containing the desired compound were evaporated to give a crude product which was then crystallized from 2-propanol affording compound **23** as white prisms (0.54 g, 71%), mp 202-203°; uv (ethanol): λmax 202 (log ε = 4.24), 218 sh (4.13), 279 (4.18) nm; ir (chloroform): ν 3413 (NH), 1735 (C=O) cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.56 (s, 3H, SCH_3), 3.36 and 3.37 (each s, 3H, OCH_3), 7.27-7.80 (m, 5H, aromatic), 10.12 (bs, 1H, NH), 12.55 (s, 1H, NH); ms: m/z (relative intensity) 336 (M^+, 64), 277 (26), 230 (100).

Anal. Calcd. for $C_{14}H_{16}N_4O_4S$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.13; H, 4.91; N, 16.48.

5-(1,2-Dimethoxycarbonyl)hydrazino-4-phenyl-1*H*-imidazole (**24**).

This compound was obtained when the reduction of **17** was carried out at 95°. The product, however, was contaminated with unidentifiable substances even after repeated chromatographic purification and therefore is not satisfactory for microanalysis. Thus only the spectral data, which showed complete removal of the methylthio group of **17**, are presented as follows: ^1H nmr (dimethyl sulfoxide-d_6): δ 3.37 and 3.59 (each s, 3H, OCH_3), 7.37-7.81 (m, 5H, aromatic), 7.63 (s, 1H, H-2), 10.11 (bs, 1H, NH), 12.55 (s, 1H, NH); ms: m/z (relative intensity) 290 (M^+, 100).

1-Amino-5-(1,2-dimethoxycarbonyl)hydrazino-2-methylthio-4-phenyl-1*H*-imidazole (**13**). Acid Hydrolysis of Compound **17**.

Imidazole **17** (0.3 g) was dissolved in a mixture of ethanol and 35% aqueous hydrochloric acid (1:1 by volume, 5.0 ml) and the solution refluxed for 30 hours. After evaporation under reduced pressure, the residue was made alkaline with 5% sodium hydroxide and extracted with chloroform. The extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated. The residual solid was recrystallized twice from ethanol to give 1-aminoimidazole (**13**) as light yellow prisms (0.07 g, 29%), mp 183° with no depression on admixing with the authentic compound from imidazole **1**.

Anal. Calcd. for $C_{14}H_{17}N_5O_4S$: C, 47.86; H, 4.88; N, 19.93. Found: C, 47.78; H, 4.89; N, 19.94.

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[7] This was prepared using α-bromo-α-di-deuterioacetophenone in place of α-bromoacetophenone by the literature method [8].

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