acetaldehyde-d_4 (99+%), methanol-d_4 (99.5+%), DCl (20% in D_2O (99+%)), and D_2O (99.8%) were purchased from Aldrich. Commercially available sodium isopropylxanthate from ICN was recrystallized from acetone/ethyl acetate before use.

Thiapendione (2). A preliminary account of the synthesis of thiapendione has been given in a communication.[6a] Below is a more detailed description of its preparation.

Methyl 2,2-bis-(*O*-isopropyldithioxanthyl)acetate was readily prepared by addition of methyl dichloracetate to a suspension of 2 mol equiv of sodium isopropylxanthate in acetone at room temperature. After an initial filtration and removal of the solvent, the residual oil was extracted into hexane and filtered and the solvent removed to provide the bisxanthate as a light yellow oil suitable for further reaction.

In a 4-L beaker containing a large magnetic stir bar and thermometer is placed 1500 mL of concentrated sulfuric acid. The acid is cooled to 0 °C and 50 mL of ether is cautiously added with stirring. Methyl 2,2-bis-(*O*-isopropyldithioxanthyl)acetate (100 g) is then added dropwise to the stirred solution at such a rate that the temperature is maintained between 0 and 5 °C. After the addition, the cooling bath is removed and the temperature allowed to rise to 18 °C at which point the frothy mixture is poured onto 4 L of crushed ice, precipitating crude thiapendione as a tacky white solid. Decantation and filtration through a large coarse sintered glass funnel yield the dione, which is washed well with water and then triturated with two 100-mL portions of ice-cold ether. After drying, thiapendione is recrystallized from a minimal amount of chloroform and/or dimethoxyethane, affording 35–40 g of long white needles, mp 179–181 °C in 57-65% yield. It should be noted that thiapendione has been observed to sensitize and produce skin rashes on some individuals.

4,5-Bis(propargylthio)-1,3-dithiol-2-one (3, R = H). A solution of thiapendione (**2**; 5.0 g, 24 mmol), propargyl bromide (4.8 g, 50 mmol), and Aliquot 336 (23.5 g, 48 mmol) in benzene (300 mL) was degassed for 10 min by bubbling nitrogen through the stirred solution. Anhydrous sodium carbonate (10.6 g, 100 mmol) in 100 mL of water was added to the reaction mixture with vigorous stirring under nitrogen for 2 h at 40–45 °C. After the reaction mixture was cooled, the benzene layer was separated, washed with water, and dried over Na_2SO_4 and the solvent removed. The crude oil was chromatographed on silica gel (20/80 chloroform/hexane), yielding a clear light yellow oil: 5.0 g (82%); IR (KBr) 2925, 1940, 1672, 1265, 1235, 865 cm^{-1}; NMR ($CDCl_3$) δ 2.32 (1 H), 3.59 (2 H); MS, *m/e* 258.

Dimethylenetetrahydrotetrathiafulvalene (5, R = H). To a solution of sodium methoxide, generated by dissolving sodium (1.7 g, 76 mmol) into 80 mL of methanol, was added 5.0 g (19 mmol) of 4,5-bis(propargylthio)-1,3-dithiol-2-one (**3**). The reaction turned orange and then slowly to yellow when heated to reflux for 2 h. After cooling, the reaction was worked up by extraction with ether and water, the organic layer dried, and the solvent evaporated, leaving a yellow oil. The oil was chromatographed on silica gel (20/80 chloroform/hexane) to afford pure product as a yellow oil: 1.4 g (32%); IR (KBr) 2900, 1612, 1220, 1180, 860 cm^{-1}; NMR δ 4.00 (2 H), 5.17 (1 H), 5.27 (1 H); MS, *m/e* 220.

Dimethyltetrathiafulvalene (6, R = H). Dimethylenedihydrotetrathiafulvalene (**5**; 2.0 g, 9 mmol) was refluxed in benzene with *p*-toluenesulfonic acid (6.8 g, 36 mmol) for 2 h. On cooling the isomerized product crystallized out as bright orange solid. Recrystallization from acetonitrile yielded orange needles. All spectroscopic analysis of the product agreed with that of an authentic sample.[12]

1-(Trimethylsilyl)butyn-3-ol-d_5 (7). *n*-Butyllithium (1.6 M, 65 mL, 0.1 mol) was added dropwise to a solution of (trimethysilyl)acetylene (10 g, 0.1 mol) in THF (200 mL) with stirring under nitrogen at −40 °C. After stirring for 1 h, the solution was cooled to −50 °C and acetaldehyde-d_4 (5 g, 0.1 mol) was added in one portion. The reaction mixture was warmed to room temperature and then poured into a solution of DCl in D_2O. The organic layer was extracted with ether and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the deuterated alcohol was distilled as a clear liquid: 9.55 g (62%); bp 65 °C (15 mm); MS, *m/e* 147.

1-(Trimethylsilyl)-3-bromobutyne-d_4 (8). A solution of **7** (9.5 g, 65 mmol) in dry pyridine (6.4 mL) was added dropwise to an ether suspension of excess dibromotriphenoxyphosphorane[13] at 0 °C. The reaction was stirred at room temperature for 2 h, and then the solids were filtered and washed with ether. The filtrate was extracted with D_2O, the ether layer was separated and dried over Na_2SO_4, and the solvent removed under reduced pressure. The residual oil was distilled to afford pure bromide: 10.7 g (78%); bp 70 °C (26 mm); MS, *m/e* 209.

Tetramethyltetrathiafulvalene-d_{12} (TMTTF-d_{12}). The same experimental details described above for **6** was employed for the tetramethyl derivative. 1-(Trimethylsilyl)-3-bromobutyne-d_4 (**8**; 50 mmol) was reacted with thiapendione (**2**; 25 mmol) under phase-transfer reaction conditions in D_2O to provide 4,5-bis[1-(trimethylsilyl)butyn-3-yl]-1,3-dithiol-2-one-d_8 (**9**) which was isolated after chromatography (silica gel, 20/80 chloroform/hexane) as a clear light-yellow oil in 84% yield; MS, *m/e* 438. Treatment of **9** with 4 equiv of sodium methoxide in refluxing methanol-d_4 gave after workup perdeuterated **5** (R = CD_3) as a yellow oil in 55% yield; MS, *m/e* 272. Isomerization to TMTTF-d_{12} was affected by treatment with excess *p*-toluenesulfonic acid-*d* in refluxing benzene (2 h) from which the bright orange product precipitated. Recrystallization from acetonitrile gave orange needles; mp 241–243 °C; MS, *m/e* 272. NMR and mass spectral analysis indicated a deuterium content of ~97%.

Acknowledgment. We thank J. Mayerle for help in X-ray analysis. This work was supported in part by the Office of Naval Research.

Registry No. **3** (R = H), 88180-75-0; **5** (R = H), 88180-76-1; **5** (R = CD_3), 88180-79-4; **6a** (R = H), 54397-96-5; **6b** (R = H), 54397-97-6; **7**, 88180-77-2; **8**, 88180-78-3; **9**, 88200-32-2; TMTTF-d_{12}, 88200-33-3; CD_3CDO, 1632-89-9; $(CH_3)_3SiC{\equiv}CH$, 1066-54-2; methyl 2,2-bis(*O*-isopropyldithioxanthyl)acetate, 64407-81-4; methyl dichloroacetate, 116-54-1; sodium isopropylxanthate, 140-93-2; thiapendione, 64394-45-2; propargyl bromide, 106-96-7.

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An Improved Preparation and Use of 2-Bromoacetoacetaldehyde in a New Synthesis of 2-Substituted-4-acetylimidazoles

Christopher A. Lipinski,* Thaddeus E. Blizniak, and Rebecca H. Craig

Central Research, Pfizer Inc., Groton, Connecticut 06340

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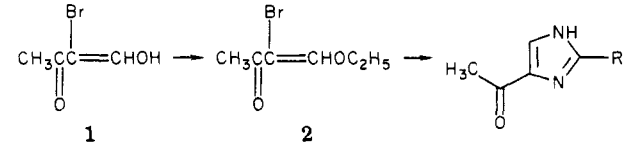
2-Bromoacetoacetaldehyde (3-bromo-4-hydroxy-3-buten-2-one, **1**) is potentially very useful as a reactive and distinctively trifunctionalized intermediate that can be regarded as a vinylogous acetic acid. In contrast to 3-bromoacetylacetone, 2-bromoacetoacetates, and the related and synthetically versatile halomalonaldehydes,[1] the utility of this reagent has not been fully realized because of the lack of a reliable synthesis. We now report a reliable



1 **2**

synthesis in over 50% yield that is capable of scaleup and

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0022-3263/84/1949-0566$01.50/0

Table I. Bromination of Sodium Acetoacetaldehyde (Na AA)

run	scale Na AA,[a] mol	solvent/ vol, mL	temp, °C	content Na AA,[b] mol %	time, h	mole ratios Na AA	mole ratios Br_2	mole ratios T NaS	isolated crystalline yield, %	mp, °C	work-up
A	0.092	CH_2Cl_2/250	−70	88	24	0.92	1.0	1.05	51.0	110-111	*d*
B	0.092	CH_2Cl_2/250	−70	88	24	0.92	1.0	1.05	53.6	109-110	*d*
C	0.092	CH_3OH/250	−70	88	24	0.92	1.0	1.05	21.7	109-110	*d*
D	0.092	THF/250	−70	88	24	0.92	1.0	1.05	13.2	92-94	*d*
E	0.092	CH_2Cl_2/250	0	88	24	0.92	1.0	1.05	42.7	112-113	*d*
F	0.092	CH_2Cl_2/250	0	88	24	0.92	1.0	1.05	43.0	112-113	*d*
G	0.092	CH_2Cl_2/250	−70	88	24	0.92	1.0	1.05	22.9	113-114	*e*
H	0.092	CH_2Cl_2/250	−70	88	24	0.92	1.0	1.05	28.1	112-113	*e*
I	0.027	H_2O/50	0	84	0.5	0.90	1.0	1.07	oil, complex NMR		*f*
J	0.360	CH_2Cl_2/750	−70	85	21	0.90	1.0	1.06	45.3	112-113	*d*
K	0.297	CH_2Cl_2/150	−70	73	22	0.81	1.0	1.11	16.3	110-114	*d*
L	0.375	CH_2Cl_2/900	−70	75	17	0.75	1.0	1.0	30.9	113-115	*d*
M	0.297	CH_2Cl_2/650	−70	75	17	1.0	1.0	1.33	55.0	115-116	*d*
N	0.297	CH_2Cl_2/305	−70	73	22	0.81	1.0	1.11	33.5	110-114	*d*
O	0.027	CH_2Cl_2/65	−70	84	4	0.90	1.0	1.07	53.0	not taken	

[a] Scale is moles of sodium acetoacetaldehyde (NA AA) in starting mixture of sodium acetoacetaldehyde plus sodium formate. [b] Content Na AA is moles of sodium acetoacetaldehyde in mixture of total sodium salt (T NaS-sodium acetoacetaldehyde plus sodium formate) as determined by NMR integration. [c] T NaS is total sodium salt (sodium acetoacetaldehyde plus sodium formate). [d] Filter, strip, CCl_4 slurry. [e] H_2O workup. [f] Ether extraction.

also illustrate the utility of the readily prepared vinylogous acetic acid ester derivative 3-bromo-4-ethoxy-3-buten-2-one (2) in a new synthesis of 2-substituted-4-acetylimidazole derivatives.

There are only two literature procedures for the synthesis of crystalline 2-bromoacetoacetaldehyde (1). In the first, Kochetkov and co-workers reported that aqueous bromination of 4,4-dimethoxy-2-butanone gave crystalline 1 in 40–51% yield.[2,3] The Kochetkov method gave in our hands a low yield of crystalline 1, which even upon isolation was unstable in water, a 10 mg/mL suspension decomposing within 2–3 min at 23 °C. Furthermore, reproducible results are difficult to obtain because success is dependent on the product oiling out of a warm aqueous system and being isolated before it decomposes. In the second method, Ichihara and co-workers prepared 1 in yields of only 3.9% and 11.9% by bromination of sodium acetoacetaldehyde in carbon tetrachloride.[4] We have modified the nonaqueous bromination of sodium acetoacetaldehyde into a preparatively more useful process by the use of exactly stoichiometric amounts of bromine based on NMR analysis of sodium acetoacetaldehyde content.

Results and Discussion

Sodium acetoacetaldehyde was prepared by formylation of acetone with ethyl formate, using sodium ethoxide in ether. A major impurity always present in our sodium acetoacetaldehyde was 10–40 mol % sodium formate, which was easily detected by NMR and was also confirmed by IR analysis. The presence of sodium formate as a contaminant leads to the generation of hydrogen bromide due to oxidation of sodium formate by bromine (eq 1).[5]

$$HCO_2Na + Br_2 \rightarrow CO_2 + NaBr + HBr \quad (1)$$

This is an important and deleterious side reaction because hydrogen bromide is known to isomerize α-bromo ketones.[6] By way of contrast bromination of pure sodium acetoacetaldehyde is a neutral reaction (eq 2).

$$CH_3COCH{=}CHONa + Br_2 \rightarrow CH_3COCBr{=}CHOH + NaBr \quad (2)$$

Table I summarizes the effect of bromine stoichiometry, solvent, temperature, and reaction time on the bromination of sodium acetoacetaldehyde. The most critical factor for success is the use of exactly stoichiometric amounts of bromine based on NMR analysis of sodium acetoacetaldehyde content (see Experimental Section). Methylene chloride is the optimal solvent since, as expected on the basis of product instability, aqueous workup decreased yields. Reaction concentration, temperature, and time are less critical parameters.

Yields were consistent in duplicate experiments (Table I; A, B; E, F; G, H) using sodium acetoacetaldehyde with 12 mol % sodium formate content. Methylene chloride is a better solvent for 2-bromoacetoacetaldehyde than is carbon tetrachloride and proved markedly advantageous as a solvent, giving higher yields than methanol (C), tetrahydrofuran (D), or water (I). Reaction at −70 °C was slower than that at 0 °C but gave somewhat higher yields (A, B vs. E, F). Reaction time at −70 °C was not a critical factor, the yield being similar after 4 or 24 h (A, B vs. O). A water workup of the reaction run under optimal conditions gave lower yields than the nonaqueous workup (G, H vs. A, B) despite attempts to minimize the period of exposure to water. The yield on scaleup from 0.1 to 0.4 mol declined only slightly (J vs. A, B).

The Claisen condensation used to prepare sodium acetoacetaldehyde is capricious and the formate content is unpredictable. When sodium acetoacetaldehyde containing greater than 15 mol % sodium formate was used, yields were decreased, particularly when the reaction was run at concentrations exceeding 1 M (K). This presents a serious problem since in 38 experiments preparing sodium acetoacetaldehyde the mean content of sodium formate was 23 mol % (range 12–100) and we were unable to reproducibly lower the content below 15 mol %. This problem was solved by experiments examining the effect of changing mol ratios of bromine (Table I; L, M, N). A

(2) Kochetkov, N. K.; Nifant'ev, E. E. *Dokl. Akad. Nauk SSSR* **1958**, *121*, 462–465; *Chem. Abstr.* **1959**, *53*, 1137*h*.
(3) Kochetkov, N. K.; Nifant'ev, E. E.; Molodtsov, N. V. *Zh. Obshch. Khim.* **1959**, *29*, 2330–2337; *Chem. Abstr.* **1960**, *54*, 14230*g*.
(4) Ichihara, A.; Maekawa, H.; Kanda, R.; Shirahama, H.; Matsumoto, T. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1158–61.
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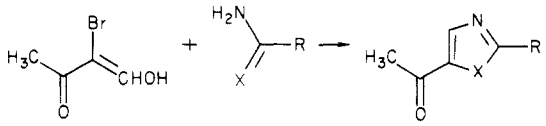
Table II. Five-Membered Acetyl Heterocycles



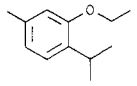
cmpd	X	R	mp, °C	crystallization solvent	mol form	yield, %
3	S	H_2N	180 dec	acetone	$C_5H_6N_2OS \cdot HBr$	55
4	O	H_2N	217-218	methanol	$C_5H_6N_2O_2$	42
5	NH	H_3C	134-135	subl 110 °C (0.01 mm)	$C_6H_8N_2O$	42
6	NH	$HOCH_2$	148-149	subl 140 °C (0.01 mm)	$C_5H_6N_2O_2$	12
7	NH	4-pyridyl	198-201	ethyl acetate	$C_{10}H_9N_3O \cdot {}^1/_3H_2O$	39
8	NH		175-176	ppt from H_2O	$C_{16}H_{20}N_2O_2$	9

Table III. Combustion Analyses

		calcd			found		
cmpd	formula	C	H	Br	C	H	Br
1	$C_4H_5BrO_2$	29.12	3.05	48.43	28.80	3.15	47.84
II	$C_4H_4Br_2O_2$	19.70	1.65	65.53	19.72	1.67	63.21
3	$C_5H_6N_2OS \cdot HBr$	26.92	3.16	12.56	27.02	3.40	12.69
4	$C_5H_6N_2O_2$	47.62	4.80	22.21	47.26	4.51	22.09
5	$C_6H_8N_2O$	58.05	6.50	22.57	57.87	6.45	22.63
6	$C_6H_8N_2O_2$	51.42	5.75	19.99	51.21	5.74	19.99
7	$C_{10}H_9N_3O \cdot {}^1/_3H_2O$	62.17	5.04	21.75	62.30	4.67	21.48
8	$C_{16}H_{20}N_2O_2$	70.56	7.40	10.29	70.16	7.07	10.29

bromine content in excess of that required to react with sodium acetoacetaldehyde (L, N) proved inferior to one in which the bromine content was exactly equimolar to that of sodium acetoacetaldehyde (M). 2,2-Dibromoacetoacetaldehyde was isolated as a minor product from a reaction run under optimal conditions.

The utility of trifunctionalized 2-bromoacetoacetaldehyde is illustrated by its use in a new imidazole synthesis. Cyclization reactions of **1** with bifunctional nucleophiles such as thiourea, urea, or amidine salts can in theory lead to formyl or acetyl five-membered ring products or to six-membered ring products. Literature reports that cyclization of **1** with thiourea or urea gives the acetyl five-membered products 2-amino-5-acetylthiazole or oxazole were reproduced[3] (Table II; **3**, **4**). Literature analogy with halomalonaldehyde chemistry[1] suggested that **1** might react with amidines to form six-membered pyrimidine products. Surprisingly, the neutral vinylogous ester derivative, 3-bromo-4-ethoxy-3-buten-2-one (**2**), which was prepared in situ from **1** in essentially quantitative yield (as determined by NMR), reacted with amidine salts in refluxing dioxane to give five-membered acetylimidazoles (Table II) rather than pyrimidines. The yield of 42% reported for **5**[7] represents an optimized yield and reflects in part the difficulty of isolation of the low-melting, water-soluble **5**, since no other significant products were detected in the reaction by TLC. The yields of **6**, **7** and **8** are not optimized, and other unisolated cyclization products may be present. The balance of factors leading to the new imidazole synthesis reported here may be subtle, and it is entirely possible that minor changes in the structure of **2** may affect the course of cyclization with amidines.

Experimental Section

^1H NMR spectra were obtained on a Varian T-60 spectrometer. ^{13}C NMR spectra were obtained on a Varian XL-100. Chemical shifts from tetramethylsilane are reported on the δ scale. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Melting points are uncorrected and were obtained in open capillaries on a Thomas-Hoover melting point apparatus. Solvent and reagents were commercially available unless otherwise noted and were used directly. Microanalyses were performed by the Analytical Department of Pfizer Inc. Where analyses are indicated only by symbols of the elements, analytical values were within ±0.4% of theoretical values (Table III).

Sodium Acetoacetaldehyde (Sodium 4-Hydroxy-3-buten-2-one). To a slurry of 54.01 g (1.0 mol) of sodium methoxide in 453.6 g of diethyl ether under nitrogen was added a solution of 58.1 g (1.0 mol) of acetone and 74.1 g (1.0 mol) of ethyl formate (both dried over Linde 3A molecular sieves). The reaction was stirred during the 30-min addition period by an efficient mechanical stirrer under nitrogen atmosphere, and the internal reaction temperature was maintained at 25–30 °C by an ice bath. Cooling below 25 °C adversely affects product quality because it slows reaction rate and leads to a very thick precipitate that is difficult to filter. After the addition was complete, stirring was continued for 15 min, and the resulting light tan solid was collected by filtration, washed with ether, and then dried under a nitrogen atmosphere to prevent water absorption. Further drying at 23 °C for 20 h in a vacuum oven gave 85.0 g of a very pale tan powder. A readily filterable, friable solid results from a successful formylation. A very thick porridge-like hygroscopic filtrate indicates a poor reaction and on drying gives clumps of salt, which brominate poorly. The mole fraction of sodium 4-hydroxy-3-buten-2-one to sodium formate is conveniently monitored by NMR; 50 mg of salt is dissolved in 0.5 mL of D_2O at 23 °C and the spectrum is taken within 15 min of solution. The mole fraction of sodium acetoacetaldehyde to sodium formate is determined by the ratio of integrals of the single proton absorbances at δ 8.75 to those at δ 8.33. In the representative experiment described here, the integral ratio of sodium acetoacetaldehyde is 0.85 and is calculated from the integral at δ 8.75 divided by the sum of integrals at δ 8.75 and δ 8.33. In 38 experiments the mean mole fraction of sodium acetoacetaldehyde was 0.77 ± 0.11. In four experiments only sodium formate was isolated: ^1H NMR (D_2O) δ 8.75 (d, 0.85 × 1, J = 11 Hz, =CHONa), 8.33 (s, 0.15 × 1, O=CHONa), 5.13 (d, 0.85 × 1, J = 11 Hz, COCH=), 2.12 (s, 0.85 × 3, CH_3). The doublet at δ 8.75 collapses partially to a broad singlet due to H–D exchange of the H at δ 5.13 over a typical time period required to run a spectrum (15–30 min after solution). However, the relative integrals of protons at δ 8.75 and 8.33 remain unchanged over at least 4 h at 23 °C. The content of sodium

(7) LaMattina, J. L.; Lipinski, C. A. European Patent 50-458, 1982.

formate was confirmed by a somewhat less convenient IR analysis: IR (KBr) (sodium acetoacetaldehyde) 1350, 770 cm^{-1} (band absent); IR (KBr) (sodium formate) 1350, 770 cm^{-1} (strong).

2-Bromoacetoacetaldehyde (3-Bromo-4-hydroxy-3-buten-2-one, 1). The following bromination procedure is applicable to batches of sodium acetoacetaldehyde containing up to 35 mol % sodium formate. Sodium acetoacetaldehyde containing greater than 35 mol % sodium formate should be discarded. To 850 mL of methylene chloride was added 81.5 g of crude sodium acetoacetaldehyde that had been finely ground in a mortar and pestle (mole fraction 0.868, (81.5 ÷ (0.868(108) + 0.132(68)) × 0.868 = 0.69 mol). The slurry was cooled to −70 °C, and to the stirred slurry was added 110 g (0.69 mol) of bromine in 50 mL of methylene chloride over 15 min. The reaction was stirred at −70 °C for 20 h and allowed to warm to 23 °C. The very pale yellow reaction was filtered, and the white to pale-tan filter cake was washed with 500 mL of warm methylene chloride. The combined yellow filtrates were concentrated on a rotary evaporator at 25 °C to a solid residue, which was triturated with carbon tetrachloride. The yellow filtrate may change to red as the methylene chloride is being concentrated, but yield is not affected provided that the filtrate is not excessively heated during the concentration procedure. The solid was collected by filtration and dried in vacuo at 23 °C to give 63.5 g (56%) of 2-bromoacetoacetaldehyde: mp 112–113 °C; ^1H NMR (Me_2SO) δ 10.57 (br s, 1, OH), 8.33 (s, 1, CHO), 2.33 (s, 3, CH_3); ^{13}C NMR (Me_2SO, 100 MHz) δ 25.41 (q, CH_3), 103.71 (s, CBr), 160.38 (d, CHO), 188.45 (s, CO). An analytical sample was prepared by crystallization from carbon tetrachloride: mp 115–116 °C (lit.[2] mp 109–110 °C). Anal. Calcd for $C_4H_5BrO_2$: C, 29.12; H, 3.05; Br, 48.43. Found: C, 28.80; H, 3.15; Br, 47.84.

2,2-Dibromoacetoacetaldehyde (II). The carbon tetrachloride mother liquors from trituration of crude 1 were repeatedly concentrated in vacuo and cooled to remove small additional quantities of 1. The ^1H NMR spectrum of the resulting red oil showed two new singlet peaks in addition to those attributable to 1. Rapid evaporative distillation (80 °C, 0.01 mmHg) gave 6.65 g of a clear pale yellow oil, which slowly evolved hydrogen bromide and partially solidified after several hours at 0 °C: ^1H NMR ($CDCl_3$) δ 9.33 (s, 1, CHO), 2.62 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.43 (q, CH_3), 65.65 (d, CBr_2, long-range coupling to CHO), 182.13 (d, CHO), 193.77 (s, CO). Anal. Calcd for $C_4H_4Br_2O_2$: C, 19.70; H, 1.65; Br, 65.53. Found: C, 19.72; H, 1.67; Br, 63.21.

2-Amino-5-acetylthiazole Hydrobromide (3). A 0.825-g (5 mmol) sample of 2-bromoacetoacetaldehyde was dissolved in 35 mL of acetone and cooled to 0 °C, and 0.381 g (5 mmol) of thiourea was added. Solution occurred within a few minutes. The reaction was allowed to warm to 23 °C. After 30 min a slight precipitate was noted and the reaction was allowed to stir at 23 °C for 20 h and then heated at reflux for 1 h. On cooling to 23 °C, a solid formed and was collected by filtration to give 0.608 g (55%) of 2-amino-5-acetylthiazole hydrobromide, mp 169–171 °C with decomposition. An analytical sample was prepared by trituration with isopropyl alcohol: mp 167(softens)–180 °C dec (lit.[2] mp 176–178 °C); ^1H NMR (Me_2SO) δ 10.17 (br s, 3), 8.35 (s, 1), 2.47 (s, 3). Anal. ($C_5H_6N_2OS \cdot HBr$) C, H, N.

2-Amino-5-acetyloxazole (4). To 15 mL of acetone were added 1.1 g (6.7 mmol) of 2-bromoacetoacetaldehyde and 1.0 g (16.7 mmol) of urea. The slurry was stirred at 23 °C for 1 h, and the pale orange reaction was heated at reflux for 45 min during which time the color changed to a deep red and a red oil came out of the solution. The reaction was cooled in ice, and the acetone was decanted from the oil, which had solidified. The oily solid was dissolved in a minimum of water and brought to pH 10 with concentrated NH_4OH, and the resultant orange-yellow solid was collected by filtration, washed with water, and dried to give 0.35 g (42%) of 2-amino-5-acetyloxazole, mp 205–210 °C. An analytical sample was prepared by crystallization from methanol: mp 217–218 °C (lit.[2] mp 210–211.5 °C); ^1H NMR (Me_2SO) δ 7.78 (s, 1), 7.6 (br s, 2), 2.23 (s, 3). Anal. ($C_5H_6N_2O_2$) C, H, N.

3-Bromo-4-ethoxy-3-buten-2-one (2). To a solution of 800 mL of absolute ethanol and 175 mL of dry toluene was added 41.2 g (0.25 mol) 2-bromoacetoacetaldehyde. The solution was heated at reflux over 2.5 h, and during this time solvent was gradually removed. The solution was cooled and concentrated in vacuo to an oil: ^1H NMR (Me_2SO) δ 7.87 (s, 1), 4.32 (q, 2), 2.43 (s, 3), 1.65 (t, 3).

2-Methyl-4-acetylimidazole (5). The oily vinylogous ester 2 (46.7 g, 0.24 mol) was combined with 28.6 g of acetamidine acetate (0.24 mol) and 19.8 g (0.24 mol) of anhydrous sodium acetate in 1 L of 1,4-dioxane and was heated at reflux for 60 h. The reaction was cooled and solid was removed by filtration. The dioxane solution was concentrated in vacuo to an oily solid, which was dissolved in 200 mL of water and brought to pH 10 with concentrated $NaHCO_3$ solution. The solution was decolorized with activated charcoal and concentrated in vacuo to a solid. This material was slurried in $CHCl_3$, and solid was removed by filtration. The $CHCl_3$ solution was concentrated in vacuo to a heavy oil. Trituration with ethyl acetate gave 12.44 g (42%) of 2-methyl-4-acetylimidazole[7] as a yellow solid; mp softens 122 °C, melts 127–128 °C. An analytical sample was prepared by sublimation at 110 °C (0.01 mmHg): mp 134–135 °C; ^1H NMR (Me_2SO) δ 9.52 (br s, 1), 7.68 (s, 1), 2.37 (s, 3), 2.33 (s, 3). Anal. ($C_6H_8N_2O$) C, H, N.

2-(Hydroxymethyl)-4-acetylimidazole (6). To a solution of 300 mL of absolute ethanol and 60 mL of dry toluene was added 16.5 g (0.1 mol) of 2-bromoacetoacetaldehyde. The solution was heated at reflux, and over 2.5 h solvent was removed. The reaction was cooled and concentrated in vacuo to give 19.3 g of oil. To the oil was added 300 mL of 1,4-dioxane, 11.0 g (0.1 mol) hydroxyacetamidine hydrochloride,[8] and 16.4 g (0.2 mol) of anhydrous sodium acetate. The reaction was heated at reflux for 20 h and cooled, and solid was removed by filtration. Concentration of the dioxane solution gave an oil, which was partitioned between ethyl acetate and water. The water layer was concentrated in vacuo to an oil, which was chromatographed on silica gel by using 10% methanol in chloroform as eluent to give 1.7 g (12%) of 2-(hydroxymethyl)-4-acetylimidazole:[7] mp 148–149 °C; ^1H NMR (Me_2SO) δ 10.8 (v br s by integration, 1), 7.37 (s, 1), 5.5 (v br s by integration, 1), 4.5 (s, 2), 2.38 (s, 3). An analytical sample was prepared by sublimation at 140 °C (0.01 mmHg); mp 148–149 °C. Anal. ($C_6H_8N_2O_2$) C, H, N.

2-(4-Pyridyl)-4-acetylimidazole (7). To a solution of 120 mL of absolute ethanol and 10 mL of dry toluene was added 1.46 g (8.9 mmol) of 2-bromoacetoacetaldehyde. The solution was heated at reflux, and over 2.5 h solvent was removed. The reaction was cooled and concentrated in vacuo to an oil. To the oil was added 1.40 g (18.9 mmol) of isonicotinamidine hydrochloride[9] and 1.46 g (17.8 mmol) anhydrous sodium acetate in 45 mL of 1,4-dioxane. The slurry was heated at reflux for 2 h and cooled, and solid was removed by filtration. The dioxane solution was concentrated in vacuo to a solid, which was dissolved in 40 mL of water and the pH adjusted to 7 with solid sodium bicarbonate. Following extraction with ethyl acetate to remove less polar impurities, the aqueous solution was concentrated in vacuo to a foam and then triturated with 3 mL of ethanol–20 mL of ethyl acetate to give a yellow solid. This was isolated by filtration, washed with ethyl acetate, and dried to give 0.65 g (39%) of 2-(4-pyridyl)-4-acetylimidazole: mp 190–195 °C; ^1H NMR (Me_2SO) δ 8.7 (d, 2), 8.1 (s, 1), 7.79 (d, 2), 7.0 (v br s by integration, 1), 2.52 (s, 3). An analytical sample was prepared by crystallization from ethyl acetate; mp 198–201 °C. Differential thermal analysis showed an endothermic transition at 115 °C (water loss) and melt at 204 °C. Anal. ($C_{10}H_9N_3O \cdot {}^1/_3H_2O$) C, H, N.

2-[(Thymyloxy)methyl]-4-acetylimidazole (8). To a solution of 150 mL of absolute ethanol and 20 mL of dry toluene was added 4.5 g (27.3 mmol) of 2-bromoacetoacetaldehyde. The solution was heated at reflux, and over 2.5 h solvent was removed. The reaction was cooled and concentrated in vacuo to 5.3 g of oil. To the oil was added 6.0 g (24.7 mmol) of (thymyloxy)acetamidine hydrochloride[10] and 2.0 g (24.7 mmol) of anhydrous sodium acetate in 100 mL of 1,4-dioxane. The reaction was heated at reflux for 60 h and cooled, and solid was removed by filtration. The dioxane solution was concentrated in vacuo to an oil. Addition of a small volume of water gave a solid, which was collected by filtration. The solid was taken up in methanol and decolorized with charcoal,

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(9) Poziomek, E. J. *J. Org. Chem.* **1963**, *28*, 590–591.
(10) Bader, H.; Downer, J. D. *J. Chem. Soc.* **1953**, 1636–1640.

and the methanol was removed in vacuo to give 2.62 g of crude 2-[(thymyloxy)methyl]-4-acetylimidazole hydrochloride: mp 163–166 °C; ^{1}H NMR (Me_2SO) δ 7.87 (s, 1), 7.1–6.5 (m, 3), 5.03 (s, 2), 3.17 (m, 1), 2.43 (s, 3), 2.27 (s, 3), 2.77 (d, 6). This material was dissolved in hot water and the pH was brought to 9 with solid sodium bicarbonate. A solid formed and was collected by filtration and dried to give 0.58 g (9%) of 2-[(thymyloxy)methyl]-4-acetylimidazole; mp 175–176 °C. Anal. ($C_{16}H_{20}N_2O_2$) C, H, N.

Registry No. 1, 87005-15-0; 3, 88158-39-8; 4, 87005-17-2; 5, 78210-66-9; 6, 82982-60-3; 7, 88158-40-1; 8, 88158-41-2; 3-bromo-4-ethoxy-3-buten-2-one, 82982-59-0; 2,2-dibromoacetoacetaldehyde, 82176-32-7; sodium methoxide, 124-41-4; acetone, 67-64-1; ethyl formate, 109-94-4; sodium 4-hydroxy-3-buten-2-one, 14975-15-6; acetamidine acetate, 36896-17-0; hydroxyacetamidine hydrochloride, 54198-71-9; isonicotinamidine hydrochloride, 1452-60-4; (thymyloxy)acetamidine hydrochloride, 20287-83-6; 2-[(thymyloxy)methyl]-4-acetylimidazole, 88158-42-3.

On the Distribution of Products in the Degenerate Rearrangement of Doubly Labeled Triarylvinyl Cations[1]

Zvi Rappoport*

Department of Organic Chemistry, The Hebrew University, Jerusalem 91904, Israel

Charles Y. Fiakpui, Xian-Da Yu, and Choi Chuck Lee*

Department of Chemistry, University of Saskatchewan, Saskatoon, Saskatchewan, Canada S7N 0W0

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Lee and co-workers have described recently some double labeling experiments on the solvolysis–rearrangement of 1,2-diphenyl-2-[$^2H_5$]phenyl[2-^{13}C]vinyl bromide (**1**) in 70% HOAc–30% H_2O.[2] From mass spectrometric analyses of the four isotopomeric benzophenones obtained from reduction and cleavage of the solvolysis products, the distribution of the product-forming isotopomeric triphenylvinyl cations **2–5** (Scheme I) was deduced to be **2** (84.7 ± 2.2%)/**3** (7.3 ± 1.2%)/**4** (6.6 ± 1.2%)/**5** (1.5 ± 0.5%). Analysis of the ^{13}C NMR spectra showed a 15.2 ± 0.5% scrambling of ^{13}C from C-2 to C-1.

In a qualitative interpretation of the above results, it was suggested[2] that if half of the initially formed cation **2** were equilibrated between **2** and **4** and the other half equilibrated between **2**, **3**, and **5**, then "complete equilibration" for such a mechanism would give rise to a distribution of products of 58.3%, 16.7%, 16.7%, and 8.3%, respectively, from cations **2–5**. Since the observed results did not agree with this distribution, it was concluded that equilibration among the various isotopomeric triphenylvinyl cations was not complete in the solvolysis of **1**, but the observed presence of some product from **5** was regarded as a definite demonstration of the occurrence of successive 1,2 shifts in the triphenylvinyl cation.[2]

One of us (Z.R.) has pointed out to the Canadian group (Lee et al.) that the assumption that **2** should equilibrate half with **4** and half with **3** and **5** may be incorrect. In analyzing the formation of products from the precursor isotopomeric cations **2–5**, one is dealing not only with equilibration but also with capture of these cations vs. their equilibration. A more quantitative interpretation of the double-labeling results may be obtained by using a steady-state treatment of Scheme I, with both the scrambling processes and product-forming capture reactions taken into account. Such a steady-state treatment, neglecting isotope effects and assuming that $k_{Ph} = k_{Ph}^*$ and that the rate constants (k_{SOH}) for the capture of **2–5** are identical, gives eq 1 for the relative ratios of **2–5** in terms **2/3/4/5** =

$$1.0:(2+\alpha)/[(2+\alpha)^2-2]:1/(2+\alpha):1/[(2+\alpha)^2-2] \quad (1)$$

of the capture vs. rearrangement ratio α ($\alpha = k_{SOH}/k_{Ph}$). Consequently, when $k_{SOH} \gg k_{Ph}$, i.e., α is large so that $(2+\alpha)^2 \gg 2$, the **[3]/[4]** ratio will be very close to unity. For example, when $\alpha = 8$, the **[3]/[4]** ratio will be 1.02, and even when $\alpha = 3$, the **[3]/[4]** ratio is 1.09. In the solvolysis of **1**,[2] the results showed approximately equal amounts of products derived from **3** (7.3 ± 1.2%) and from **4** (6.6 ± 1.2%). This near equality of products from **3** and **4** thus reflects a high value for α and is not the result of half of **2** equilibrated with **4** and the other half equilibrated with **3** and **5**.

The assumptions that $k_{Ph} = k_{Ph}^*$ and that k_{SOH} is identical for the capture of **2–5** are equivalent to assuming that the cationic species **2–5** are similar, or at least behave similarly. A possible alternative is the presence of a "memory effect", which will be reflected in different behaviors of the different cations according to their method of formation. For example, the initially formed **2** may differ in the position of the counterion from **5** which is formed only after two consecutive 1,2 shifts, and this may result in different k_{SOH} or k_{Ph} values for the two ions. In order to decide between the alternatives, we compared the observed and the calculated product distributions. By using an α value of 9.2,[3] which is based on 15.2% scrambling for the solvolysis in 70% HOAc–30% H_2O of triphenylvinyl bromide singly labeled at C-2 with ^{13}C or ^{14}C[2,4] and the relative ratios derived from the steady-state treatment as given by eq 1, the calculated distribution of products from the various isotopomeric cations is **2** (84.2%)/**3** (7.6%)/**4** (7.5%)/**5** (0.7%). These values are in excellent agreement with the observed results, except that the value for **5** is lower. Since the percentage of **5** is very low and the associated error is large, we believe that the deviation is mechanistically insignificant. We, therefore, conclude that the assumption that consecutive 1,2 shifts take place in structurally identical isotopomeric cations is quantitatively validated. A similar labeling analysis which requires the formation of a tetracyclic carbocation by consecutive rearrangements starting from an isotopomeric cation was described by Goldstein and Warren.[5] However, in their system the cationic species involved in the rearrangement are isotopic diastereomers, whereas in our system they are simple isotopomers.

Lee and co-workers[6] have extended the double labeling work to include a study on a doubly labeled trianisylvinyl cationic system. 1,2-Dianisyl-2-(*p*-[$^2H_3$]methoxyphenyl)[2-^{13}C]vinyl bromide (**6**) was solvolyzed in 70% HOAc–30% H_2O without or with the presence of 1, 5, 10, or 400 equiv of added NaOAc. The products were degraded to dianisyl ketone and analyzed by mass spec-

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