May 1994 Notes Chem. Pharm. Bull. 42(5) 1149—1150 (1994) 1149

Reaction of Enaminones with Benzyltrimethylammmonium Dichloroiodate

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Received November 10, 1993; accepted January 6, 1994

Reaction of enaminones with benzyltrimethylammonium dichloroiodate (BTMA·ICl_2) in methylene chloride–methanol in the presence of sodium bicarbonate at room temperature gave iodinated products at the α-position of the carbonyl group in good yields within 1 h.

Keywords enaminone; heterocyclic compound; iodination; benzyltrimethylammonium dichloroiodate; iodine–silver trifluoroacetate

Kajigaeshi *et al.* prepared benzyltrimethylammonium dichloroiodate (BTMA·ICl_2) (**1**) from benzyltrimethylammonium chloride and iodine monochloride in good yield,[1] and used the reagent successfully for the iodination of a wide range of aromatic compounds, such as phenols,[1] aromatic amines,[2] and acetanilide derivatives.[3] Compared with viscous iodine monochloride, which is commonly used for iodination reaction, BTMA·ICl_2 is easy to use quantitatively, because it is a solid (stable yellow crystals, mp 125—126 °C).

In the course of our synthetic studies of biologically active heterocyclic compounds,[4] we needed the iodinated enaminone **2**. For iodination of enaminones, Habermehl *et al.*[5] reported the preparation of **4** from **3** by the action of iodine in methylene chloride in low yield (13%). Therefore, we tried to use BTMA·ICl_2 for iodination of **3**. Thus, a solution of **3** in methylene chloride–methanol was treated with BTMA·ICl_2 (1 eq) in the presence of sodium bicarbonate at room temperature. The reaction was very fast. After 10 min, a TLC check showed no starting enaminone **3**. After removal of the insoluble materials, saturated sodium bicarbonate solution was added and the whole was extracted with chloroform. Recrystallization of the crude product from 2-propanol–hexane gave **4** in 81% yield. We then tried to use BTMA·ICl_2 for preparation of our desired compound **2**. When the reaction of **5a**, prepared easily by dehydration between dimedone and aniline, with BTMA·ICl_2 was performed under the same reaction conditions as above, the desired compound **2a** was obtained in 74% yield. Some other enaminones (**5b, c** and **6a—c**) were also synthesized (Table I), and their iodination reactions were examined; good results were obtained except for **6c**. The reaction conditions of the iodination reactions and some physical data of the products are shown in Table II. In the case of **6c**, the reaction resulted in the formation of a complex mixture, from which 16% of the starting material (**6c**) was recovered. When 6a was treated with 2 eq of BTMA·ICl_2 in the same solvent system at room temperature for 1 h, **7a** was isolated in 82% yield and no product iodinated on the phenyl ring was detected. Finally, treatment of **6a** with iodine in chloroform in the presence of silver trifluoro-

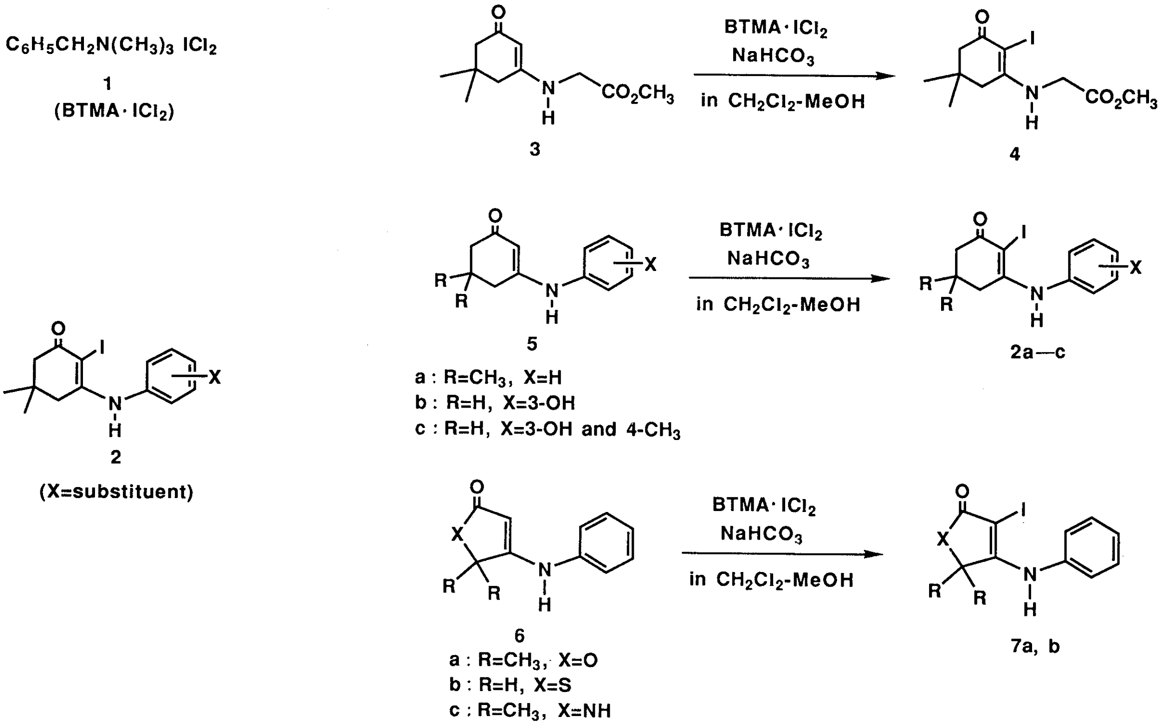

Chart 1

TABLE I. Yields and Physical Data of **3**, **5a**—**c** and **6a**—**c**

Compd.	R	X	Yield (%)	mp (°C) (Recryst. solvent)	Analysis (%) Found (Calcd) C	H	N
3[5]			77	124—125			
				($CHCl_3$–hexane)			
5a	CH_3	H	87	185—188	78.07	7.88	6.55
				(2-PrOH–hexane)	(78.11	7.96	6.51)
5b	H	3-OH	88	188—189	70.78	6.50	6.87
				(2-PrOH–hexane)	(70.92	6.45	6.89)
5c	H	3-OH, $4-CH_3$	81	267.5—269.5	71.74	6.94	6.40
				(EtOH)	(71.87	6.96	6.45)
6a	CH_3	O	80	261—263	71.17	6.61	6.79
				(EtOH–hexane)	(70.92	6.45	6.89)
6b	H	S	89	253—255	62.66	4.75	7.29
				(Acetone)	(62.80	4.74	7.32)
6c	CH_3	NH	78	290—293	71.19	6.90	13.80
				(2-PrOH–hexane)	(71.26	6.98	13.85)

TABLE II. Reaction Conditions for the Iodination of Enaminones with BTMA·ICl_2 and Yields of **2a**—**c**, **4** and **7a**, **b**

Compd.	R	X	BTMA·ICl_2 (eq)	Temperature	Time (min)	Yield (%)
2a	CH_3	H	1	r.t.	40	74
2b	H	3-OH	1	r.t.	60	66
2c	H	3-OH, $4-CH_3$	1	r.t.	80	68
4[5]			1	r.t.	10	81
7a	CH_3	O	1	r.t.	10	89
			2	r.t.	60	82
7b	H	S	1	r.t.	20	82

r.t. = room temperature.

acetate at room temperature for 3 h gave **7a** in 75% yield, though silver trifluoroacetate is relatively expensive. In summary, BTMA·ICl_2 is a convenient and effective iodinating reagent at the α-position of the carbonyl group of a wide range of enaminones.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus, model MP-S3, and are uncorrected. Infrared (IR) spectra were measured with a Hitachi 260-30 infrared spectrometer, and proton nuclear magnetic resonance (^1H-NMR) spectra were recorded on a JEOL JNM-FX270 (270 MHz) spectrometer using tetramethylsilane as an internal standard.

5,5-Dimethyl-3-(phenylamino)-2-cyclohexen-1-one (5a) Aniline (6.5 ml, 71 mmol) and *p*-toluenesulfonic acid monohydrate (catalytic amount) were added to a solution of dimedone (10.0 g, 71 mmol) in benzene (70 ml). This mixture was refluxed with stirring for 3 h. During the reaction, the water formed was removed azeotropically using a Dean–Stark trap. Precipitates formed upon cooling were collected by filtration and recrystallized from 2-propanol–hexane to give 10.89 g of **5a** as pale yellow prisms. Additional **5a** (2.434 g) was obtained from the filtrate and the total yield was 87%, mp 185—188 °C. IR (Nujol): 3200, 1590, 1570 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.10 (6H, s, 2 × CH_3), 2.22 and 2.35 (each 2H, s, CH_2), 5.58 (1H, s, =CH–), 6.46 (1H, br s, NH), 7.12—7.37 (5H, m, ArH). Microanalytical data are shown in Table I.

Other enaminones (**3**,[5] **5b**, **c** and **6a**—**c**) were prepared similarly, and the results are listed in Table I. 5,5-Dimethyltetronic acid and 5,5-dimethyltetramic acid were synthesized by the reported procedure,[6] and thiotetronic acid is commercially available.

2-Iodo-5,5-dimethyl-3-(phenylamino)-2-cyclohexen-1-one (2a) BTMA·ICl_2 (0.81 g, 2.3 mmol) was added to a solution of **5a** (0.50 g, 2.3 mmol) in methylene chloride (35 ml) and methanol (25 ml). After addition of sodium bicarbonate (1.30 g, 15.5 mmol), the whole was stirred at room temperature for 40 min. The color of the reaction mixture changed from turbid yellow to colorless. Insoluble materials were removed by filtration and washed with methanol. The combined solution of the filtrate and the washings was concentrated under reduced pressure and the residue was treated with a saturated solution of sodium bicarbonate. This mixture was extracted three times with chloroform, and the combined organic layer was washed with water and brine, successively. After drying over anhydrous sodium sulfate, the organic layer was concentrated under reduced pressure to give the crude product, which was purified by recrystallization from 2-propanol–hexane. Pure **2a** (0.456 g) was obtained as colorless needles. Additional **2a** (0.216 g) was obtained from the filtrate and the total yield was 74%, mp 163—164 °C. IR (Nujol): 3200, 1620, 1590, 1555 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.04 (6H, s, 2 × CH_3), 2.42 and 2.48 (each 2H, s, CH_2), 3.4 (1H, br s, NH), 7.11—7.47 (5H, m, ArH). *Anal.* Calcd for $C_{14}H_{16}INO$: C, 49.28; H, 4.73; N, 3.72. Found: C, 49.02; H, 4.68; N, 4.02.

Other compounds (**2b**, **c**, **4** and **7a**, **b**) were obtained similarly. Molar equivalents of BTMA·ICl_2 used, reaction temperature, reaction time, yield, and melting point are summarized in Table II.

3-(3-Hydroxyphenylamino)-2-iodo-2-cyclohexen-1-one (2b) mp 158.5—159.5 °C (2-PrOH–hexane). IR (Nujol): 3250, 1600, 1575, 1555, 1535 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.80 (2H, m, CH_2), 2.43 (2H, t, J = 6.0 Hz, CH_2), 2.54 (2H, t, J = 6.0 Hz, CH_2), 6.60—6.71 (3H, m, ArH), 7.17 (1H, t, J = 8.0 Hz, ArH), 8.01 (1H, br s, OH), 9.46 (1H, br s, NH). *Anal.* Calcd for $C_{12}H_{12}INO_2$: C, 43.79; H, 3.67; N, 4.26. Found: C, 43.69; H, 3.65; N, 4.08.

3-(3-Hydroxy-4-methylphenylamino)-2-iodo-2-cyclohexen-1-one (2c) mp 165—166 °C (EtOH). IR (Nujol): 3230, 1590, 1550 cm^{-1}. ^1H-NMR (DMSO-d_6) δ: 1.71 (2H, m, CH_2), 2.12 (3H, s, $ArCH_3$), 2.39—2.54 (4H, m, 2 × CH_2), 6.57 (1H, dd, J = 8.0, 2.0 Hz, ArH), 6.62 (1H, d, J = 2.0 Hz, ArH), 7.06 (1H, d, J = 8.0 Hz, ArH), 7.97 (1H, br s, NH), 9.33 (1H, s, OH). *Anal.* Calcd for $C_{13}H_{14}INO_2$: C, 45.50; H, 4.11; N, 4.08. Found: C, 45.34; H, 4.17; N, 3.85.

2-Iodo-3-(methoxycarbonylmethylamino)-5,5-dimethyl-2-cyclohexen-1-one (4) mp 94—96 °C (CH_2Cl_2–hexane) (lit.[5] 88—91 °C). IR (Nujol): 3250, 1740, 1615, 1580, 1565, 1530 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.09 (6H, s, 2 × CH_3), 2.38 (2H, s, CH_2), 2.43 (2H, s, CH_2), 3.83 (3H, s, OCH_3), 4.12 (2H, d, J = 6.0 Hz, NCH_2CO), 6.16 (1H, br s, NH). *Anal.* Calcd for $C_{11}H_{16}INO_3$: C, 39.19; H, 4.78; N, 4.15. Found: C, 39.14; H, 4.63; N, 3.85.

2-Iodo-4,4-dimethyl-3-(phenylamino)-2-buten-4-olide (7a) mp 219—223 °C (2-PrOH–hexane). IR (Nujol): 3230, 1695, 1590, 1550, 1535, 1500 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.51 (6H, s, 2 × CH_3), 6.42 (1H, br s, NH), 7.18—7.47 (5H, m, ArH). *Anal.* Calcd for $C_{12}H_{12}INO_2$: C, 43.79; H, 3.67; N, 4.26. Found: C, 43.73; H, 3.69; N, 4.17.

2-Iodo-3-(phenylamino)-2-butene-4-thiolide (7b) BTMA·ICl_2 (0.364 g, 1.1 mmol) and sodium bicarbonate (0.587 g, 7.0 mmol) were added to a suspension of **6b** (0.20 g, 1.1 mmol) in methylene chloride (19.4 ml) and methanol (7.8 ml), mp 104—106 °C (chloroform–hexane). IR (Nujol): 3260, 1660, 1585, 1570 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.05 (2H, s, CH_2), 7.12 (1H, br s, NH), 7.18—7.52 (5H, m, ArH). *Anal.* Calcd for $C_{10}H_8INOS$: C, 37.87; H, 2.54; N, 4.42. Found: C, 37.76; H, 2.68; N, 4.37.

Reaction of 6a with Iodine and Silver Trifluoroacetate A solution of iodine (0.125 g, 0.5 mmol) in chloroform (6.4 ml) was added dropwise to a stirred suspension of **6a** (0.100 g, 0.5 mmol) and silver trifluoroacetate (0.111 g, 0.5 mmol) in chloroform (1.6 ml) at room temperature over a period of 2 h. The reaction mixture was stirred at the same temperature for an additional one hour. Insoluble materials were removed by filtration and the filtrate was washed with a saturated solution of sodium bicarbonate, water and brine, successively. Drying over anhydrous sodium sulfate and concentration of the organic layer gave a residue, which was recrystallized from 2-propanol–hexane to give 0.122 g of pure **7a** (75%).

References and Notes

1) S. Kajigaeshi, T. Kakinami, H. Yamasaki, S. Fujisaki, M. Kondo, T. Okamoto, *Chem. Lett.*, **1987**, 2109.
2) S. Kajigaeshi, T. Kakinami, H. Yamasaki, S. Fiujisaki, T. Okamoto, *Bull. Chem. Soc. Jpn.*, **61**, 600 (1988).
3) S. Kajigaeshi, T. Kakinami, F. Watanabe, T. Okamoto, *Bull. Chem. Soc. Jpn.*, **62**, 1349 (1989).
4) K. Matsuo, K. Takahashi, T. Arase, *Chem. Express*, **8**, 373 (1993), and references cited therein.
5) G. G. Habermehl, I. Wippermann, H. C. Krebs, S. T. Dieck, *Z. Naturforsch.*, **46B**, 1415 (1991).
6) K. Matsuo, K. Tanaka, *Chem. Pharm. Bull.*, **32**, 3724 (1984).