Synthesis of 3-(Dibromoacetyl)tropolone and its Reactions with Thioureas and Thioamides

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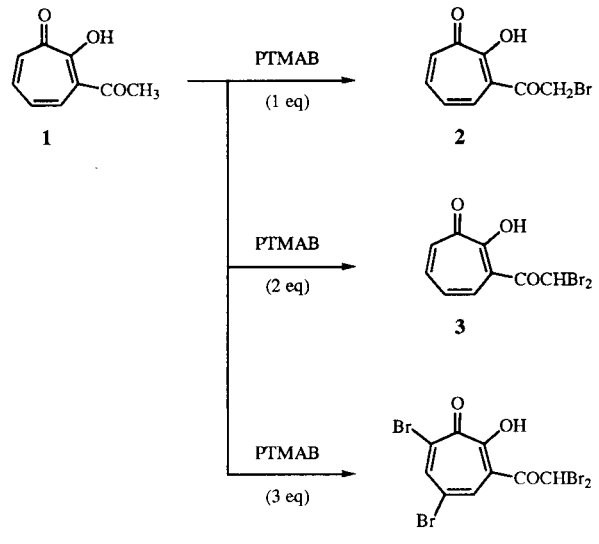
Received August 30, 1994

3-(Dibromoacetyl)tropolone (**3**) was obtained in the reaction of 3-acetyltropolone with two equimolar amounts of phenyltrimethylammonium tribromide. This tropolone **3** reacted with thiourea, 1-methyl-2-thiourea, and 1-phenyl-2-thiourea to afford *N*-unsubstituted and *N*-methyl- or *N*-phenyl-substituted 3-(2-amino-4-thiazolyl)tropolones. The reactions of **3** with thioacetamide and thiobenzamide gave 3-(2-methyl- and 2-phenyl-4-thiazolyl)tropolones.

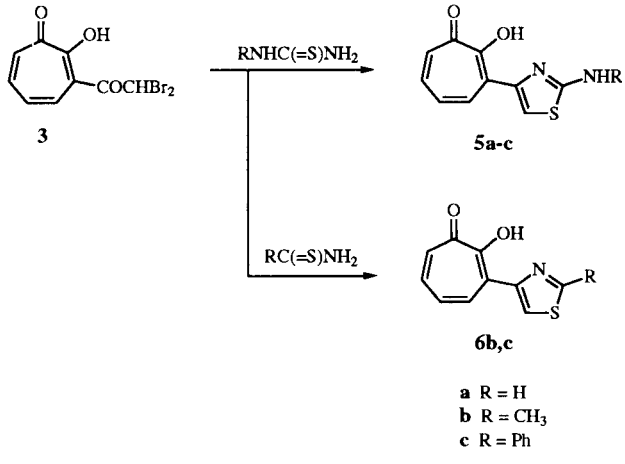
J. Heterocyclic Chem., **32**, 349 (1995).

It is well-known that the reaction of tropolone with bromine yielded brominated products at 3-, 5-, and/or 7-position. Similarly, 3-acetyltropolone (**1**) reacted with bromine to give 5,7-dibromotropolone [1]. On the other hand, we used phenyltrimethylammonium tribromide (PTMAB) as the brominating agent in tetrahydrofuran and obtained 3-(bromoacetyl)tropolone (**2**). We found that this compound **2** is useful for synthesis of tropolones having a variety of substituents in a side-chain, such as 3-(4-thiazolyl)tropolones [2] and 3-[(phenyl- and heteroarylthio)acetyl]tropolones [3]. However, compound **2** is very unstable and changed to intractable material even in a refrigerator. Thus, we newly prepared 3-(dibromoacetyl)-tropolone (**3**) and investigated its chemical behaviors. This paper deals with these results.

Scheme 1



Scheme 2



Results and Discussion.

Preparation of 3-(Dibromoacetyl)tropolone (3).

Previously, we found that, in the reaction of 3-acetyltropolone (**1**) with PTMAB, the reaction in an aprotic solvent, tetrahydrofuran, yielded 3-(bromoacetyl)tropolone (**2**) [2], while the reaction in a protic solvent, methanol-dichloromethane, yielded 7-bromo- and 5,7-dibromo-substituted 3-acetyltropolone [4]. 3-Acetyltropolone (**1**) was treated with an equimolar amount of PTMAB in tetrahydrofuran to give 3-(bromoacetyl)tropolone (**2**). Then, in the bromination of 3-acetyltropolone (**1**), the use of two equivalents of PTMAB gave 3-(dibromoacetyl)tropolone (**3**) in a yield of 73% as yellow prisms. The ^{1}H nmr spectrum shows a singlet signal at δ 7.36 for COCH proton and multiplet signals at δ 7.1-8.15 for ring-protons. In the mass spectrum, three typical isotope peaks were observed at m/z 320 (M^+), 322 [$(M+2)^+$], and 324 [$(M+4)^+$] in a ratio of 1:2:1. Thus, 3-(dibromoacetyl)tropolone (**3**) was obtained as very stable yellow crystals and might be stored at room temperature. Furthermore, when more than three equivalents of PTMAB was used, 5,7-dibromo-3-(dibromoacetyl)tropolone (**4**) was isolated in a yield of 36% as yellowish orange prisms. The ^{1}H nmr spectrum shows a singlet signal at δ 7.52 for COCH proton and two doublet peaks (J = 2 Hz) at δ 8.30 and 8.71 for 6-H and 4-H, respectively. The mass spectrum also shows five isotope peaks at m/z 476, 478, 480, 482, and 484. These data

support the structure of the compound **4** as well as elemental analysis. This compound **4** was also obtained by the bromination of 3-(dibromoacetyl)tropolone (**3**) with PTMAB in methanolic solvent.

Reactions of 3-(Dibromoacetyl)tropolone (**3**) with Thioureas and Thioamides.

Previously, we reported the synthesis of 3-(4-thiazolyl)-tropolones in 60-80% yields by using 3-(bromoacetyl)-tropolone (**2**). However, compound **2** was very unstable. Thus, we attempted to use more stable 3-(dibromoacetyl)-tropolone (**3**). On the other hand, it was reported as an unusual observation that the reactions of 1-(dibromoacetyl)-4-methoxybenzene and 6-(dibromoacetyl)-2,2-dimethyl-7-methoxychroman with thiourea gave respectively 2-amino-4-(4-methoxyphenyl)thiazole and 2-amino-4-(2,2-dimethyl-7-methoxychroman-2-yl)thiazole instead of the corresponding bromo-substituted thiazoles [5].

Although the reaction of 3-(dibromoacetyl)tropolone (**3**) with an equimolar amount of thiourea was carried out according to the conditions in the literature [2], the desired 3-(2-amino-4-thiazolyl)tropolone was not isolated. Then, one and half molar equivalents of thiourea was used. The reaction mixture was refluxing for 4 hours to afford 3-(2-amino-4-thiazolyl)tropolone (**5a**) [2] in a 19% yield. Similarly, the reactions with 1-methyl- and 1-phenyl-2-thiourea gave the corresponding 3-(2-methylamino- or 2-anilino-4-thiazolyl)tropolone **5b,c** [2] in 25 and 8% yields, respectively. The reactions of compound **3** with thioacetamide and thiobenzamide were also carried out to give 3-(2-methyl- and 2-phenyl-4-thiazolyl)tropolone **6b,c** [2] in 32 and 24% yields, respectively. The yields were lower than those of the reactions using 3-(bromoacetyl)-tropolone (**2**). This is attributed to formation of intractable materials which are inseparable. A point of advantage for the compound **3** might be its stability.

EXPERIMENTAL

The melting points were determined with a Yanagimoto MP-S2 apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded with a JEOL JNM-GX400 (400 MHz) spectrometer. A JEOL JNM-PMX60SI (60 MHz) was also used for the ^1H nmr spectra. The mass spectra were measured on a JEOL JMS-DX300 spectrometer.

Bromination of 3-Acetyltropolone (**1**) with PTMAB.

To a solution of 3-acetyltropolone (**1**) (2.0 g, 12 mmoles) in tetrahydrofuran (40 ml) was added PTMAB [4.5 g (12 mmoles), 9.0 g (24 mmoles), or 13.5 g (36 mmoles)] little by little in a period of 20 minutes at room temperature. After stirring for 30 minutes, cold water (120 ml) was added to the reaction mixture. A precipitate was collected and washed with cold water. A solution of the dried precipitate in chloroform was diluted with light petroleum to give 3-(bromoacetyl)tropolone (**2**), 3-(dibromoacetyl)tropolone (**3**), or 5,7-dibromo-3-(dibromoacetyl)-tropolone (**4**), respectively, according to the amount of PTMAB.

3-(Bromoacetyl)tropolone (**2**).

This compound was obtained from the reaction of **1** (2.0 g, 12 mmoles) with PTMAB (4.5 g, 12 mmoles), yield 1.8 g (61%), mp 137-139° (lit [2], 136-137°; ^{13}C nmr (deuteriochloroform): δ 35.6 (CH_2), 118.9, 127.5, 135.5 (3-C), 140.9, 141.0, 169.7 (1- or 2-C), 173.4 (1- or 2-C), 196.0 (C=O).

3-(Dibromoacetyl)tropolone (**3**).

This compound was obtained from the reaction of **1** (2.0 g, 12 mmoles) with PTMAB (9.0 g, 24 mmoles), yield 2.8 g (73%), yellow prisms, mp 110-112°; ir (chloroform): ν max 3016 (OH), 1713 (COCH), 1603 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 7.1-8.15 (4H, m), 7.36 (1H, s, COCH); ^{13}C nmr (deuteriochloroform): δ 43.8 ($CHBr_2$), 118.7, 127.8, 135.3 (3-C), 141.6, 142.1, 168.9 (1- or 2-C), 173.8 (1- or 2-C), 196.0 (C=O); ms: m/z (%) 324 (M+4, 2), 322 (M+2, 6), 320 (M, 2), 243 [(M+2)-^{79}Br, 51], 241 (M-^{79}Br, 53), 149 (100).

Anal. Calcd. for $C_9H_6Br_2O_3$: C, 33.57; H, 1.88%. Found: C, 33.87; H, 1.98%.

5,7-Dibromo-3-(dibromoacetyl)tropolone (**4**).

a) This compound was obtained from the reaction of **1** (2.0 g, 12 mmoles) with PTMAB (13.5 g, 36 mmoles), yield 2.02 g (36%), yellowish orange prisms, mp 130-137°; ir (potassium bromide): ν max 3060 (OH), 1698 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 7.52 (1H, s, COCH), 8.30 (1H, d, J = 2 Hz, 6-H), 8.71 (1H, d, J = 2 Hz, 4-H); ms: m/z (%) 484 (M+8, 0.6), 482 (M+6, 2.4), 480 (M+4, 3.7), 478 (M+2, 2.4), 476 (M, 0.6), 402 (16), 400 (40), 398 (39), 396 (13), 322 (17), 320 (33), 318 (17), 309 (20), 307 (40), 305 (21).

Anal. Calcd. for $C_9H_4Br_4O_3$: C, 22.53; H, 0.84%. Found: C, 22.53; H, 0.95%.

b) To a solution of the compound **3** (300 mg, 0.94 mmole) in methanol (10 ml)-dichloromethane (2 ml) was added PTMAB (700 mg, 2 mmoles) little by little. The mixture was stirred for 30 minutes at room temperature and worked up, as described above, to give the compound **4**, yield 170 mg (38%).

Reactions of 3-(Dibromoacetyl)tropolone (**3**).

To a solution of 3-(dibromoacetyl)tropolone (**3**) (515 mg, 1.6 mmoles) in absolute ethanol (50 ml) was added thiourea (2.4 mmoles). A mixed solution was refluxed for 4 hours. The mixture was concentrated and a precipitate was collected and recrystallized from ethanol to give 3-(2-amino-4-thiazolyl)-tropolones **5a-c**.

3-(2-Amino-4-thiazolyl)tropolone (**5a**).

This compound was obtained from the reaction with thiourea in a yield of 66 mg (19%), mp 248-251° (lit [2], mp 251-252°).

3-(2-Methylamino-4-thiazolyl)tropolone (**5b**).

This compound was obtained from the reaction with 1-methyl-2-thiourea in a yield of 92 mg (25%), mp 210-212° (lit [2], 212-214°).

3-(2-Anilino-4-thiazolyl)tropolone (**5c**).

This compound was obtained from the reaction with 1-phenyl-2-thiourea in a yield of 40 mg (8%), mp 188-192° (lit

[2], 191-192°).

Reactions of 3-(Dibromoacetyl)tropolone (**3**) with Thioamides.

A solution of 3-(dibromoacetyl)tropolone (**3**) (515 mg, 1.6 mmoles) and thioamide (2.4 mmoles) in absolute ethanol (50 ml) was refluxed for 4 hours. The reaction mixture was worked up, as described above, and recrystallized from ethanol to give 3-(4-thiazolyl)tropolones **6b,c**.

3-(2-Methyl-4-thiazolyl)tropolone (**6b**).

This compound was obtained from the reaction with thioacetamide in a yield of 111 mg (32%), mp 108-117° (lit [2], 127-129°).

3-(2-Phenyl-4-thiazolyl)tropolone (**6c**).

This compound was obtained from the reaction with thiobenzamide in a yield of 107 mg (24%), mp 144-147° (lit [2], 148-149°).

Acknowledgement.

We wish to thank Dr. T. Kurihara, Josai University, for his kind measurements of the mass spectra.

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