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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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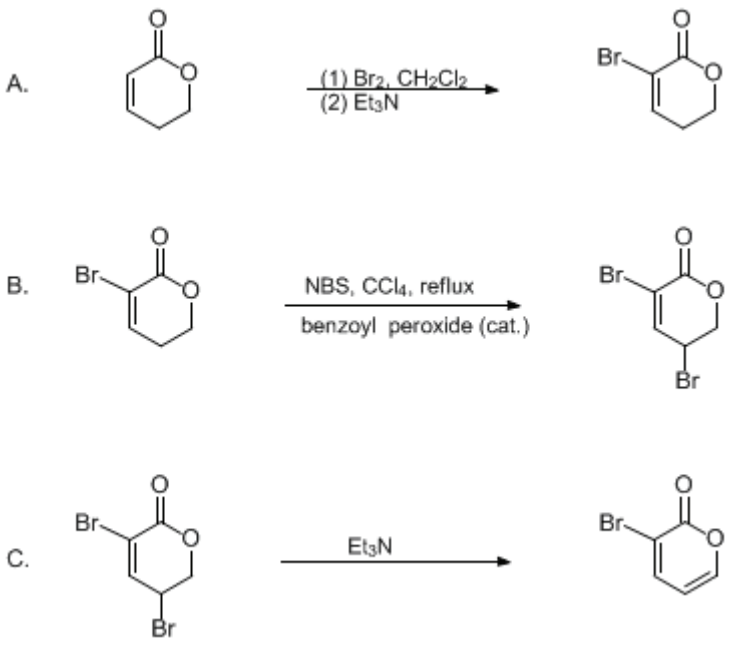
AN IMPROVED PREPARATION OF 3-BROMO-2H-PYRAN-2-ONE: AN AMBIPHILIC DIENE FOR DIELS-ALDER CYCLOADDITIONS

[2H-Pyran-2-one, 3-bromo-]



Submitted by G. H. Posner, K. Afarinkia, and H. Dai[1].
Checked by Alyx-Caroline Guevel and David J. Hart.

1. Procedure

A. *3-Bromo-5,6-dihydro-2H-pyran-2-one*. A 1-L, three-necked, round-bottomed flask, equipped with a magnetic stirring bar, a pressure-equalizing addition funnel, a drying tube that contains sodium hydroxide pellets, and a thermometer, is charged with 10.15 g (0.103 mol) of 5,6-dihydro-2H-pyran-2-one (Note 1) and 350 mL of methylene chloride (Note 2). The addition funnel is charged with a solution of 16.7 g (0.105 mol) of bromine (Note 3) in 130 mL of methylene chloride. The bromine solution is added over a period of 4 hr (Note 4) in 10–15-mL portions (*Caution! Exothermic reaction. External cooling may be necessary*). After the addition of the last portion of bromine, the reaction is analyzed by TLC and NMR (Note 5) and (Note 6). The resulting pale orange solution is stirred for 2 hr until the color has almost faded. The addition funnel is replaced by a rubber septum, and the reaction mixture is cooled by means of an ice bath. Via syringe, 15.0 mL (0.107 mol) of triethylamine is added through the rubber septum over 2 min (*Caution! Exothermic reaction*). The colorless solution is stirred for 40 min and then the contents of the flask are transferred to a 1-L separatory funnel and washed twice with 150 mL of water. The organic phase is dried over anhydrous sodium sulfate and filtered through a pad of silica gel (Note 7) and the pad rinsed with 700 mL of methylene chloride. The combined filtrates are concentrated at reduced pressure (20 mm) and the last traces of solvent are removed under high vacuum at ambient temperature to afford 16.3 g (89%) of 3-bromo-5,6-dihydro-2H-pyran-2-one as an amber-colored mobile liquid that solidifies when stored overnight at −4°C. This material is sufficiently pure for use in the next step. An analytically pure sample may be prepared by Kugelröhr distillation at 1.0 mm (pot temperature 100°C) (Note 8).

B. *3,5-Dibromo-5,6-dihydro-2H-pyran-2-one*. A flame-dried, 1-L, round-bottomed flask, equipped with a magnetic stirring bar and an efficient water-cooled condenser fitted with a nitrogen inlet, is placed under a nitrogen atmosphere and charged with 15.8 g (0.089 mol) of 3-bromo-5,6-dihydro-2H-pyran-2-one, 16.5 g (0.093 mol) of N-bromosuccinimide (Note 1), 0.8 g (3.3 mmol) of benzoyl peroxide

(Note 1), and 455 mL of freshly distilled carbon tetrachloride. The reaction flask is immersed in a preheated oil bath (100°C) and the contents are refluxed vigorously for 4.5 hr (Note 9) and (Note 10); the reaction mixture is cooled and allowed to stand at room temperature for 4.5 hr. The precipitate (9.5 g) is collected by suction filtration, the filtrate is concentrated under reduced pressure at 50–60°C (20 mm), and the last traces of solvent are removed under high vacuum (1 mm) at room temperature over 2.5 hr affording 21.5 g (94%) of crude 3,5-dibromo-5,6-dihydro-2H-pyran-2-one as an amber liquid which is sufficiently pure for use in the next step (Note 11). This crude material may be further purified by chromatography (Note 12).

C. *3-Bromo-2H-pyran-2-one*. A 1-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, and rubber septum through which a needle-tipped inert gas line is inserted (vented through a mineral oil bubbler), is charged with 20.3 g of crude 3,5-dibromo-5,6-dihydro-2H-pyran-2-one, as prepared above, and 360 mL of methylene chloride (Note 1). Via syringe, 14.0 mL (0.1 mol) of triethylamine (Note 2) is added over a 5-min period at room temperature. During the addition, the reaction mixture becomes dark brown. After 24 hr, analysis by TLC and NMR indicates the reaction to be complete. The reaction mixture is transferred to a 1-L separatory funnel and washed three times with 140 mL of water. The organic phase is dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure at 50–60°C (20 mm). The last traces of solvent and triethylamine are removed by brief exposure (10 min) to high vacuum at ambient temperature (Note 13). The residue is purified by chromatography on a 5.0 cm-in-diameter column of 150 g of silica gel packed in hexane. The crude material is dissolved in a minimum amount of methylene chloride and applied to the column. Elution with 800 mL of 10% ethyl acetate in hexane followed by 1300 mL of 20% ethyl acetate in hexane, using analytical TLC to monitor fractions, affords in sequence 1.97 g (14%) of 5-bromo-2-pyrone as a light-brown solid with mp 54–56°C (lit.[2] mp 60–61°C) (Note 14), and 6.06 g (43%) of 3-bromo-2-pyrone as a tan solid with mp 59.5–61°C (lit.[3,4] mp 63.5–65°C), 36% yield overall from 5,6-dihydro-2H-pyran-2-one (Note 15) and (Note 16).

2. Notes

1. All commercially available reagents were used as received without further purification. Benzoyl peroxide was 95% pure by iodometric titration.
2. All common reagents were dried according to recommended procedures[5] and were redistilled prior to use.
3. The weight of bromine should be measured by addition to a cooled, pre-weighed Erlenmeyer flask containing methylene chloride. *Caution: bromine is toxic and should always be handled in a well-ventilated fumehood*.
4. The rate of addition is determined by the temperature of the reaction mixture and the quality of the starting pyrone. In a duplicate run, starting from redistilled starting material, addition took only 2 hr.
5. TLC analysis was carried out on precoated plastic silica gel plates (with fluorescent indicator) using diethyl ether as eluant. With this eluant, the R_f of starting material is 0.50 and the R_f of 3,4-dibromo-3,4,5,6-tetrahydro-2H-pyran-2-one is 0.83. In addition to these two spots, a third spot, R_f = 0.55, corresponding to 3-bromo-5,6-dihydro-2H-pyran-2-one was detected. TLC analysis is not always reliable and it is better to analyze a small aliquot by NMR.
6. More bromine may be necessary. *Avoid addition of more bromine if the starting material has already been consumed*.
7. A pad of 100 g of flash silica gel (1.5 cm thick and 11 cm diameter) was used.
8. Distillation of 1.71 g of crude material afforded 1.50 g of pure 3-bromo-5,6-dihydro-2H-pyran-2-one as a colorless oil which solidifies at −4°C (mp 27–30°C), and which slowly turns yellow upon standing at room temperature. The spectral data for 3-bromo-5,6-dihydro-2H-pyran-2-one are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.58 (dt, 2 H, J = 6.1, 4.6), 4.49 (t, 2 H, J = 6.1), 7.30 (t, 1 H, J = 4.6); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 26.5, 66.7, 113.3, 146.2, 159.1; IR (neat) cm^{-1}: 1733, 1615; Mass spectrum (m/z) (EI, 70 eV) 177.9 and 176.9 (M^+, 42). Anal. Calcd for $C_5H_5O_2Br$: C, 33.91; H, 2.85; Br, 45.16. Found C, 33.99; H, 2.88; Br, 45.08.
9. Shortly after refluxing begins, the reaction mixture turns dark orange; however, the color dissipates by the end of the reaction period.
10. Completion of the reaction was checked by TLC analysis (Note 5). The R_f of the product is 0.60 with diethyl ether as eluant.

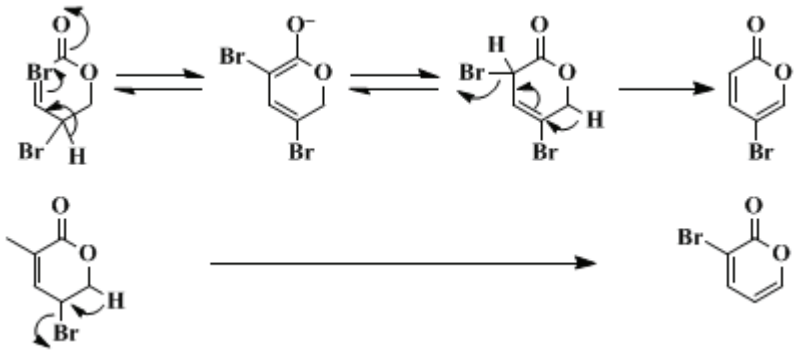
11. The crude material is contaminated with starting bromide, small amounts of succinimide and aromatic material, as well as other minor impurities as indicated by ^{1}H NMR.
12. Chromatography of 1.17 g of this material on 50 g of silica gel with elution by a gradient of 20–50% ethyl acetate in hexane gave 0.90 g (77%) of ~94% pure 3,5-dibromo-5,6-dihydro-2H-pyran-2-one as a yellow oil that crystallized on standing (mp 60.5–62.5°C; lit.[3] mp 64–65°C). The spectral data for 3,5-dibromo-5,6-dihydro-2H-pyran-2-one are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.62–4.67 (m, 1 H), 4.76–4.81 (m, 2 H), 7.37 (d, 1 H, J = 5.7). This material was contaminated with 6% of 3-bromo-5,6-dihydro-2H-pyrone as indicated by ^{1}H NMR.
13. 3-Bromo-2-pyrone sublimes in high vacuum at relatively low temperature. Thus, the material should not be subjected to high vacuum for long periods of time.
14. The spectral data for 5-bromo-2-pyrone are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.31 (dd, 1 H, J = 9.8, 1.1), 7.38 (dd, 1 H, J = 9.8, 2.7), 7.62 (dd, 1 H, J = 2.7, 1.1); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 100.7, 117.4, 145.9, 149.6, 159.3.
15. The spectral data for 3-bromo-2-pyrone are as follows: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.15 (dd, 1 H, J = 6.9, 5.0), 7.51 (dd, 1 H, J = 5.0, 1.9), 7.69 (dd, J = 6.9, 1.9); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 106.5, 112.6, 144.0, 150.1, 158.0.
16. The checkers also isolated 0.7 g (3%) of 3,5-dibromo-2-pyrone as a brown solid, mp 55.5–58.5°C (lit.[2] mp 66–67°C), from the fractions preceding the 5-bromo-2H-pyrone

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described above allows a more efficient and convenient synthesis of 3-bromo-2-pyrone than previously described in the literature.[4] This procedure avoids making and handling 2-pyrone, a sensitive compound.[6] The major by-product of the reaction is 5-bromo-2-pyrone. We postulate that the formation of this by-product results from prototropic migration in basic medium followed by elimination of HBr (Scheme 1).



3-Bromo-2-pyrone is not only a valuable precursor for the synthesis of various 3-substituted 2-pyrones,[7] [8] but it is also a reactive unsymmetrical diene.[9] [10] [11] [12] [13] 3-Bromo-2-pyrone undergoes Diels-Alder cycloadditions with a regioselectivity and stereoselectivity that is superior to that of 2-pyrone. Furthermore, 3-bromo-2-pyrone is a chameleon (i.e., ambiphilic) dienophile, undergoing cycloaddition to both electron deficient and electron rich dienophiles. The cycloadducts of bromopyrone with dienophiles are isolable and are useful in the synthesis of diastereomerically pure cyclohexene carboxylates (Scheme 2).[9,10,11,12,13]

Z = CH_2OSiMe_2-t-Bu: (i) Acrolein (10 equiv), 90°C, 96 hr, 70%; then $NaBH_4$, MeOH, 0°C, 15 min (80%); then TSDMSTf, Et_3N, CH_2Cl_2, 30 min (90%); (ii) Bu_3SnH, AIBN, benzene, reflux 2 hr (99%); (iii) MeONa, MeOH, 0°C, 92%.

Z = $OSiPh_2Me$: (i) CH_2=CHO$SiPh_2Me$ (10 equiv), 90°C, 140 hr, 44%; (ii) Bu_3SnH, AIBN, benzene, reflux 2 hr (47%); (iii) MeOLi, MeOH, 0°C, 90%.

References and Notes

1. Department of Chemistry, The Johns Hopkins University, Baltimore, MD 21218. We thank the NIH (GM-30052) for financial support.
2. Pirkle, W. H.; Dines, M. *J. Org. Chem.* **1969**, *34*, 2239.
3. Bock, K.; Pedersen, C.; Rasmussen, P. *Acta Chem. Scan.* **1975**, *29B*, 389.
4. Pirkle, W. H.; Dines, M. *J. Heterocyclic Chem.* **1969**, *6*, 1.
5. Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. "Purification of Laboratory Chemicals," 2nd ed.; Pergamon Press: New York, 1980.
6. Nakagawa, M.; Saegusa, J.; Tonozuka, M.; Obi, M.; Kiuchi, M.; Hino, T.; Ban, Y. *Org. Synth., Coll. Vol. VI* **1988** 462.
7. Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041;
8. Posner, G. H.; Nelson, T. D.; Kinter, C. K.; Johnson, N. *J. Org. Chem.* **1992**, *57*, 4083.
9. Posner, G. H.; Nelson, T. D.; Kinter, C. M.; Afarinkia, K. *Tetrahedron Lett.* **1991**, *32*, 5295;
10. For a review of 2-pyrone cycloadditions see: Afarinkia, K.; Vinader, M. V.; Nelson, T. D.; Posner, G. H. *Tetrahedron Report* **1992**, *48*, 9111;
11. For applications to synthesis of vitamin D_3 analogs, see Posner, G. H.; Dai, H. *BioMed. Chem. Lett.*, **1993**, *3* 1829;
12. For cycloadditions using 5-bromo-2-pyrone, see Afarinkia, K.; Posner, G. H. *Tetrahedron Lett.* **1992**, *33*, 7839;
13. For an improved procedure for preparation of 3-bromo-2-pyrone, see Posner, G. H.; Lee, J. K.; White, M. C.; Hutchings, R. H.; Dai, H.; Kachinski, J. L.; Dolan, P.; Kensler, T. W. *J. Org. Chem.* **1997**, *62*, 3299.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

TSDMSTf

Et_3N

Bu_3SnH

AIBN

MeONa

MeOLi

Benzene (71-43-2)

ethyl acetate (141-78-6)

MeOH (67-56-1)

diethyl ether (60-29-7)

Acrolein (107-02-8)

bromide (24959-67-9)

HBr (10035-10-6)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

methylene chloride,
CH_2Cl_2 (75-09-2)

benzoyl peroxide (94-36-0)

N-bromosuccinimide (128-08-5)

hexane (110-54-3)

triethylamine (121-44-8)

$NaBH_4$ (16940-66-2)

2-pyrone (504-31-4)

3-Bromo-2H-pyran-2-one,
3-bromo-2-pyrone,
2H-Pyran-2-one, 3-bromo- (19978-32-6)

3-Bromo-5,6-dihydro-2H-pyran-2-one,
3-bromo-5,6-dihydro-2H-pyrone (104184-64-7)

5,6-Dihydro-2H-pyran-2-one (3393-45-1)

3,5-Dibromo-5,6-dihydro-2H-pyran-2-one (56207-18-2)

5-bromo-2-pyrone,
5-bromo-2H-pyrone (19978-33-7)

3,4-dibromo-3,4,5,6-tetrahydro-2H-pyran-2-one

3,5-dibromo-2-pyrone

vitamin D_3