Organic Syntheses

Preparation of 3,5-Dibromo-2-pyrone from Coumalic Acid

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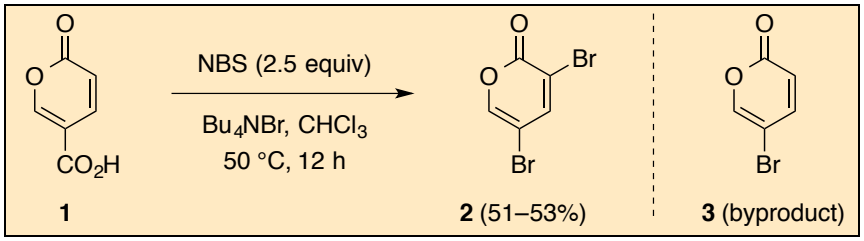
Checked by Arata Nishii and Keisuke Suzuki



Procedure

3,5-Dibromo-2-pyrone (**2**). A 200-mL two-necked round-bottomed flask, equipped with a 4.5-cm Teflon-coated magnetic stir bar and a reflux condenser, is sequentially charged with *N*-bromosuccinimide (15.8 g, 88.9 mmol, 2.5 equiv) (Note 1), tetrabutylammonium bromide (571 mg, 1.77 mmol, 0.05 equiv) (Note 2), and chloroform (50 mL) (Note 3). Coumalic acid (**1**) (5.00 g, 35.7 mmol) (Notes 4 and 5) is added to the stirring solution, which is heated by using an oil bath at 50 °C for 12 h (Note 6). After cooling to rt, hexane (100 mL) is added. The resultant two-phase mixture becomes one-phase after vigorous stirring. To remove the succinimide byproduct, the resulting mixture is filtered through a short plug of silica gel (50 g) eluting with 1400 mL of 1:1 dichloromethane–hexane, until TLC analysis shows that the product **2** is no longer detected in the eluent (Note 7). The filtrate is concentrated with a rotary evaporator (30 °C, 100 mmHg) (Note 8), and the resulting crude oil is purified by flash silica-gel column chromatography, eluting with hexane–dichloromethane (3:2) (Note 9). The combined eluents are concentrated with a rotary evaporator (30 °C, 100 mmHg) and further

evaporated with an oil vacuum pump at room temperature to afford 3,5-dibromo-2-pyrone (**2**, 4.66–4.73 g, 51–53%) as a pale yellow solid (Note 10).

Notes

1. *N*-Bromosuccinimide (99%) was purchased from Sigma-Aldrich Co. (checkers), Alfa Aesar (submitters) and used as received.
2. Tetrabutylammonium bromide (≥98%) was purchased from Kanto Chemical Co., Inc. (checkers), Daejung Chemicals (submitters) and used as received.
3. The checkers: Chloroform (99%) was purchased from Nacalai Tesque, Inc., hexane (≥95%) from Kanto Chemical Co., Inc., dichloromethane (≥ 99%) from ASAHI GLASS Co., Ltd. The submitters: Chloroform (99.8%) and hexane (CP) were purchased from Samchun Chemical, dichloromethane (EP) from Duksan Company.
4. The checkers and the submitters: Coumalic acid (>97.0%) was purchased from Tokyo Chemical Industry Co., Ltd. The checkers used coumalic acid as received. The submitters purified coumalic acid by the method of Wiley and Smith.[2] Coumalic acid **1** (25 g) was dissolved in methanol (200 mL) with heating. After dissolution, the solution was cooled in an ice bath. The precipitated solids were collected on a Büchner funnel with filter paper (No 20. 5 μm) and washed with 25 mL of cold methanol, which afforded pure coumalic acid (18 g).
5. After adding coumalic acid, the color of the resulting suspension is yellow (Fig. 1).

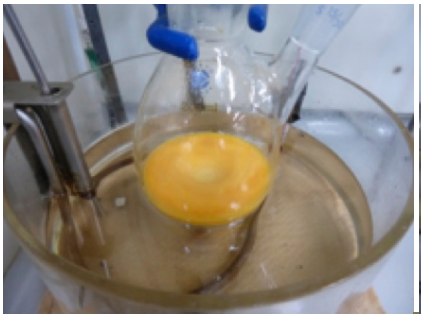


Figure 1. After 15 minutes

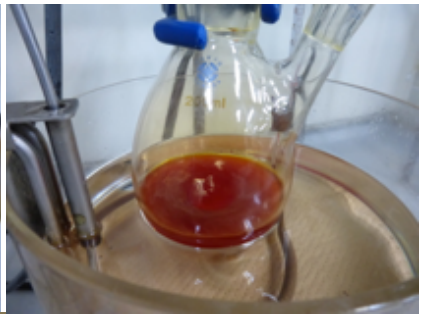


Figure 2. After 12 hours

6. After the reaction temperature increases to 50 °C, the color of the suspension turns to a reddish-orange (Fig. 2). The submitters report the observation of carbon dioxide evolution.
7. TLC analysis was performed with silica-gel plates (1.5 cm x 4 cm, glass-backed, Merck in Darmstadt, Germany), using hexane:ethyl acetate (5:1) as the eluent; R_f = 0.40. Plates were visualized by UV and a potassium permanganate stain solution.
8. Bromine is generated and evaporated during the concentration.
9. For silica-gel column chromatography, the checkers employed 0.063–0.210 mm particle size silica gel (Kanto Chemical Co., Inc., Japan), while the submitters employed 230–400 mesh, 0.040–0.063 mm particle size silica gel (Merck in Darmstadt, Germany). The crude residue was dissolved in 2:3 dichloromethane–hexane (10 mL), and the solution was charged onto a column (diameter = 6 cm) of silica gel (101 g). The column was eluted with ca. 300 mL of dichloromethane–hexane (2:3). At this point, fraction collection (100 mL fractions) was begun, and elution was continued with 2.3 L of dichloromethane–hexane (2:3). 3,5-Dibromo-2-pyrone (**2**) was obtained in fractions 4–21 (compound **2**: R_f = 0.40, hexane:ethyl acetate = 5:1). Fractions were combined and evaporated (30 °C, 100 mmHg). The fraction collection needed to be carefully performed, particularly with respect to the later fractions; a byproduct, 5-bromo-2-pyrone (**3**), runs slower on silica-gel chromatography (R_f = 0.30, hexane:ethyl acetate = 5:1), and it may contaminate the later fractions.
10. 3,5-Dibromo-2-pyrone has the following physical and spectroscopic properties: mp 63.0–64.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.59 (d, J = 2.4 Hz, 1 H), 7.74 (d, J = 2.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 99.9, 113.5, 146.6, 149.5, 156.4; IR (ATR): 3120, 3079, 1718, 1602, 1516, 1362, 1311, 1204, 1064, 973, 852 cm^{-1}; R_f = 0.40 (hexane:ethyl acetate = 5:1); Anal. Calcd. for $C_5H_2Br_2O_2$: C, 23.66; H, 0.79. Found C, 23.88; H, 0.73. The product (**2**) gradually turns to yellow when stored at rt, although the ^{1}H NMR spectrum shows no decomposition peaks. No color change is observed when the product (**2**) is stored in a refrigerator for weeks.

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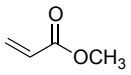
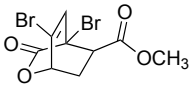
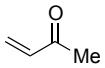
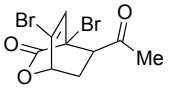
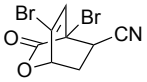
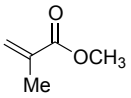
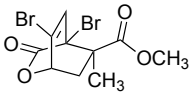
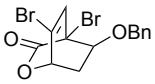
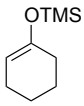
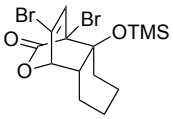
Discussion

The synthesis of 3,5-dibromo-2-pyrone was first reported by Pirkle and coworkers in 1969.[3] It was prepared from 2-pyrone (prepared from coumalic acid via thermal decarboxylation) by following either a three-step sequence that involved two successive brominations and HBr elimination or a four-step sequence that involved a bromination, HBr elimination, and photochemical bromination, followed by another HBr elimination. This

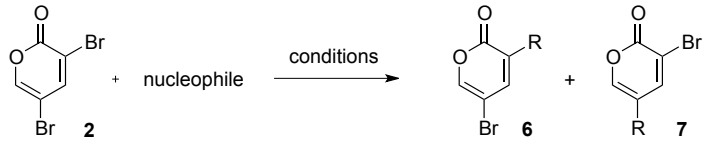
complex and even cumbersome process would the best alternative yet as there is no other method available in the literature. In this reaction, coumalic acid underwent an electrophilic aromatic bromination at C3 and bromo-decarboxylation at C5. 3,5-Dibromo-2-pyrone is a potent neutral diene that can react with both electron-poor and –rich dienophiles via either normal- or inverse-demand Diels-Alder cycloaddition reactions in good to excellent chemical yield and diastereoselectivity.[4]

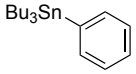
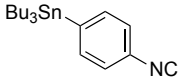
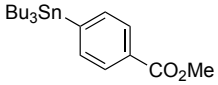
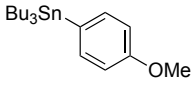
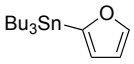
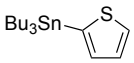
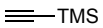
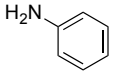
Table 1. Diels-Alder Reactions

entry	dienophile	conditions	*endo*-adduct	yield (*endo*:*exo*)
1		toluene 100 °C, 5 h		84% (94:6)
2		toluene 100 °C, 5 h		84% (94:6)
3		toluene 100 °C, 12 h		90% (76:24)
4		CH_2Cl_2, 100 °C, 24 h		84% (86:14)
5		toluene 100 °C, 3 d		69% (100:0)
6		toluene 100 °C, 2 d		73% (99:1)

Also disclosed was that either of the two C-Br groups of 3,5-dibromo-2-pyrone could be selectively mono-functionalized into the corresponding 3-substituted-5-bromo-2-pyrones **6** or 5-substituted-3-bromo-2-pyrones **7**.[5]

Table 2. Regioselective Coupling Reactions



entry	nucleophile	conditions	**6** (yield)	**7** (yield)
1		condition **A**	94%	trace
		condition **B**	trace	75%
2		condition **A**	80%	trace
		condition **B**	trace	79%
3		condition **A**	79%	trace
		condition **B**	trace	75%
4		condition **A**	61%	trace
		condition **B**	trace	55%
5		condition **A**	61%	trace
		condition **B**	trace	60%
6		condition **A**	72%	trace
		condition **B**	trace	68%
7		condition **C**	83%	trace
8		condition **D**	61%	trace

A: $Pd(PPh_3)_4$, CuI (0.1 eq), PhMe, 100 °C. **B**: $Pd(PPh_3)_4$, CuI (1.0 eq), DMF, 50 °C.
C: $Pd(PPh_3)_2Cl_2$, CuI (0.05 eq), dioxane, rt, **D**: $Pd(OAc)_2$, xantphos, Cs_2CO_3, PhMe, 110 °C

Our group has been utilizing the potent diene reactivity of both parent 3,5-dibromo-2-pyrone and the aforementioned 2-pyrone derivatives toward the synthesis of various alkaloid natural products.[6]

References

1. Department of Chemistry, Hanyang University, 222 Wangsimni-ro, Seongdong-gu, Seoul 133-791, Korea. E-mail: ccho@hanyang.ac.kr
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Appendix
Chemical Abstracts Nomenclature (Registry Number)

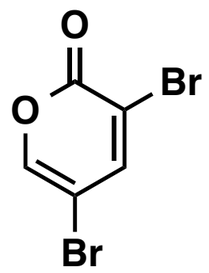
Coumalic acid: 2*H*-Pyran-5-carboxylic acid, 2-oxo-; (**1**) (500-05-0)
3,5-Dibromo-2-pyrone: 2*H*-Pyran-2-one, 3,5-dibromo-; (**2**) (19978-41-7)
5-Bromo-2-pyrone: 2*H*-Pyran-2-one, 5-bromo-; (**3**) (19978-33-7)
N-Bromosuccinimide (128-08-5)
Tetrabutylammonium bromide (1643-19-2)

Hyun-Kyu Cho was born in Seoul, Korea in 1987. He graduated in 2006 with a B.S. degree in chemistry from Hanyang University. He is currently pursuing his doctoral studies under the supervision of Prof. Cheon-Gyu Cho at the same university. His research is focused on the target-oriented total syntheses of bioactive natural products using 3,5-dibromo-2-pyrone.

Cheon-Gyu Cho was born in Seoul, Korea in 1962. He graduated in 1984 with a B.S. degree in industrial chemistry from Hanyang University. He obtained his Ph.D. from the Johns Hopkins University in 1993 (Advisor: Prof. G. H. Posner). From 1993-1996 he was a postdoctoral fellow with Prof. P. T. Lansbury at MIT. From 1996-1997 he was an instructor at Harvard Medical School. He began his independent academic career at Hanyang University in 1997. From 2004-2005 he worked with Prof. A. B. Smith at UPenn as a visiting professor. His research interests include the total synthesis of bioactive natural products and the development of new synthetic methods.

Arata Nishii was born in 1992 in Mie, Japan. He received his B.S. degree from Tokyo Institute of Technology in 2014, and is continuing his graduate studies with Professor Keisuke Suzuki. His study focuses on the synthetic method of natural products.

3,5–dibromo–2–pyrone



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DE                       10.00 use
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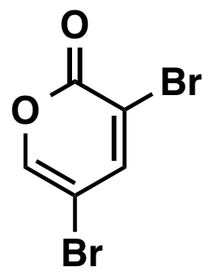
3,5–dibromo–2–pyrone



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PLW1              70.00000000 W

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PCPD2                     70.00 use
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PLW12              0.76407999 W
PLW13              0.37439999 W

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WDW                           EM
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GB                 0
PC                        1.40
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