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3-BROMO-2-PYRONE: AN EASILY PREPARED CHAMELEON DIENE AND A SYNTHETIC EQUIVALENT OF 2-PYRONE IN THERMAL DIELS-ALDER CYCLOADDITIONS

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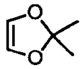
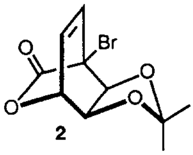
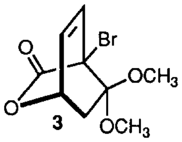
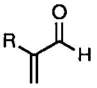
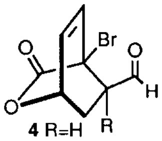
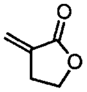
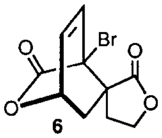
Summary. 3-Bromo-2-pyrone, a stable solid prepared by a new route (eq. 1), has been found to undergo smooth and regiospecific 2+4-cycloadditions between 78-90°C with **both** electron-rich and electron-deficient dienophiles; subsequent high-yield reductive debrominations produced halogen-free cycloadducts thus showing 3-bromo-2-pyrone to be a practical and effective synthetic equivalent of 2-pyrone in thermal Diels-Alder cycloadditions.

Diels-Alder cycloadditions of 2-pyrones usually require such high temperatures that the initial bicyclic lactone adducts often undergo cycloreversion with loss of CO_2.[1,2] High pressures (e.g., 8-19 Kbar) have occasionally been used to promote these 2+4-cycloadditions.[3] To preserve the rich stereochemistry and functionality inherent in the initial bicyclic lactone adducts, we have developed 3-sulf*in*yl- and 3-sulf*on*yl-2-pyrones as highly electron-deficient dienes that successfully undergo mild and stereocontrolled inverse-electron-demand 2+4-cycloadditions with electron-rich dienophiles such as vinylic ethers at sufficiently low temperatures to allow isolation of the initial bicycloadducts;[4] applications have been reported for synthesis of chorismic[4b] and shikimic[5] acids and of vitamin D_3.[4a] Now we have found that 3-bromo-2-pyrone (**1**), used previously by us simply as a precursor to the much more reactive (as determined by a competition experiment) 3-(*p*-toluenesulfonyl)-2-pyrone,[4] itself undergoes slow but very clean cycloaddition reactions under carefully controlled thermal conditions as an electron-deficient diene with electron-rich dienophiles and, chameleon-like, also as an electron-rich diene with electron-deficient dienophiles. As in electrophilic aromatic substitution reactions in which a bromine substituent inductively deactivates the aromatic ring but *via* resonance directs substitution to the *ortho* and *para* positions,[6] so also the bromine atom in 3-bromo-2-pyrone apparently withdraws or donates electron density to the pyrone diene unit depending on whether an electron-rich or electron-deficient dienophile is encountered. For example, a competition experiment for a limiting amount of the **electron-deficient** dienophile 2-methylene-4-butanolide indicated that 3-bromo-2-pyrone was about five times more reactive than 2-pyrone. Likewise, in a competition experiment 3-bromo-2-pyrone was found to be much more reactive than 2-pyrone toward the **electron-rich** dienophile 1,1-dimethoxyethylene.[7] Results of these regiospecific cycloadditions leading in highly stereocontrolled fashion to diverse and versatile bicycloadducts[8,9] are summarized in Table I.

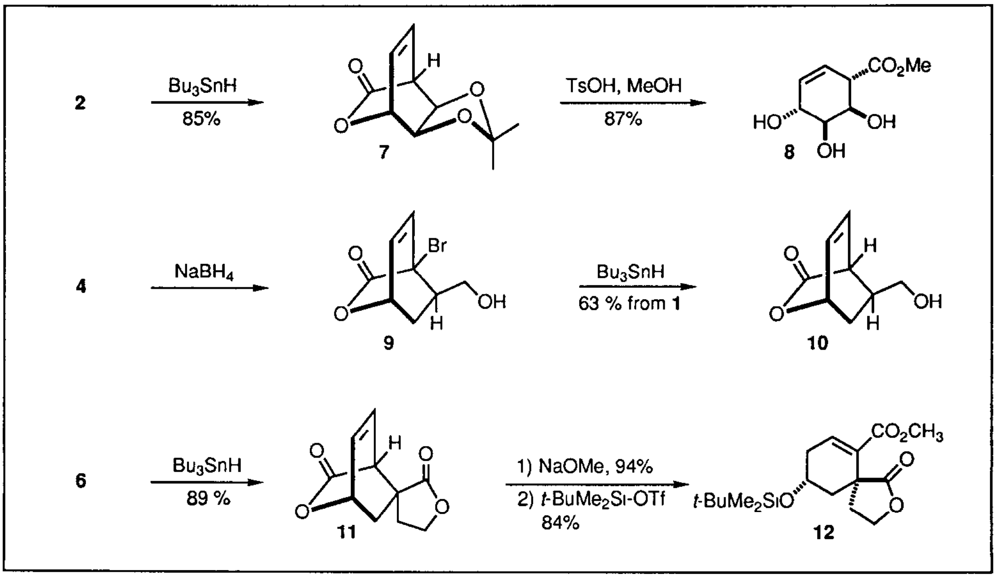
Table I

Dienophile	Conditions	endo:exo [a]	endo-Product	yield [b]
	90°C sealed tube CH_2Cl_2	4 1	 2	63 %
	80°C sealed tube CH_2Cl_2	------	 3	60 %
	sealed tube CH_2Cl_2 90°C 78°C	 >98 2 >98 2	 **4** R=H **5** R=Me	 63 % [c] 33 %
	benzene, reflux	>95 5	 6	70 %

a) based on 400 MHz ^{1}H NMR integration of crude reaction mixtures.

b) yields of purified **endo**-cycloadduct

c) this yield is based on purified product after aldehyde reduction by $NaBH_4$

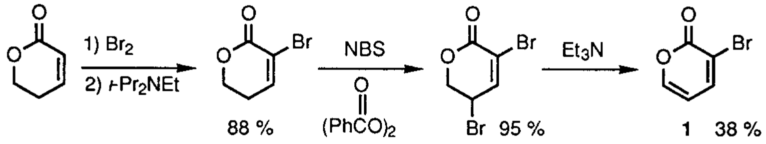


The results in Table 1 are noteworthy in several ways. First, complete and identical regiocontrol was observed with both types of dienophiles as determined by NMR decoupling and n.O.e. experiments; this clear result stands in sharp contrast, for example, to the mixture of regioisomers formed by high pressure cycloaddition of 2-pyrone with acryloyl chloride.[3a,10] Second, comparable yields of bicycloadducts were obtained with **both** electron-rich as well as electron-deficient dienophiles. Third, good to outstanding *endo*-selectivity was observed; this stereochemical assignment was based on structural correlation with chorismic acid[4b] in the case of bicycloadduct **2** and, more generally, on analogy to previous results by us[4] and by others.[3,11] Fourth, although these cycloadditions at 78-90°C required 3-4 days to reach completion, attempts to accelerate these reactions by using temperatures of ≥100°C caused decomposition of the cycloadducts.

Replacement of bridgehead bromine by hydrogen, for example in cycloadducts **2**, **9**, and **6**, proceeded smoothly and in excellent yields using tributyltin hydride and AIBN[12] to give halogen-free bicyclic lactones **7**, **10**, and **11**.[8] These bicyclic lactones can be considered to be products of formal cycloaddition of 2-pyrone itself with the various dienophiles. Thus, *via* this sequence of cycloaddition followed by reductive debromination, 3-bromo-2-pyrone is the synthetic equivalent of 2-pyrone and requires **only heat but not high pressures** for successful and regiospecific formation of bicycloadducts.

Such bicycloadducts are useful compounds for highly stereocontrolled synthesis of polyfunctionalized cyclohexenes. For example, acidic hydrolysis of the lactone unit of bicycloadduct **7** gave cyclohexene **8** in which every ring carbon atom is functionalized, and chemospecific basic methanolysis of only the bicyclic lactone moiety of dilactone **11** gave spiro-fused cyclohexene lactone **12**.[8] The high value of functionalized cyclohexenes such as **8** and **12** as versatile synthetic intermediates is obvious.[13]

Preparation of 3-bromo-2-pyrone was achieved on gram scale *via* eq. 1; this sequence of steps represents a more convenient protocol than that previously reported (the overall yields are comparable) in which purification of 3-bromo-2-pyrone was tedious and time-consuming.[14] 3-Bromo-2-pyrone is a white solid that is stable for prolonged periods at room temperature; 2-pyrone is a liquid that rapidly discolors at room temperature.



(1)

Highlights of this report include the discoveries that (1) 3-bromo-2-pyrone is sufficiently reactive upon moderate heating to form good yields of isolable cycloadducts with both (a) electron-rich dienophiles as well as with (b) electron-deficient dienophiles **with the important practical advantage over 2-pyrone of not requiring high pressures for successful cycloadditions,**[15] (2) subsequent reductive debromination proceeds in excellent yields to give halogen-free cycloadducts and therefore 3-bromo-2-pyrone is an effective synthetic equivalent of 2-pyrone; (3) these cycloadducts can be transformed smoothly into some stereochemically and functionally rich and useful synthetic intermediates, and (4) 3-bromo-2-pyrone can be prepared easily in three steps *via* a new route from commercially available 5,6-dihydro-2-pyrone.

Acknowledgment

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7. Precedent for the lack of any thermal cycloaddition between 2-pyrone and 1,1-diethoxyethylene exists: see ref. 1a.

8. New compounds were characterized spectroscopically and by combustion analysis and/or HRMS.

9. A typical experimental procedure is as follows: A flame-dried 10 mL round-bottomed flask was charged with 295 mg (1.69 mmol) 3-bromo-2-pyrone (freshly triturated from diethyl ether), 17.0 mg of barium carbonate, 3.0 mL of anhydrous benzene, and 526 mg (5.47 mmol, 3.2 eq) of 2-methylene-4-butanolide under argon and then refluxed for 36.5 hours. The reaction mixture was cooled, an additional 349 mg (3.63 mmol, 2.1 eq.) of the dienophile was added and refluxed for 40 hours. After cooling, the reaction mixture was diluted with 1:1 methylene chloride/ethyl acetate, filtered through a sintered glass funnel, the solvent removed by rotary evaporation, held under high vacuum to remove excess dienophile, and then passed through a plug of flash silica gel to give a pale white solid. This was recrystallized from ethyl acetate/hexane followed with purification of the supernatant by silica gel column chromatography to afford 321.2 mg (1.18 mmol, 70%) of the bicycloadduct **6** as a single diastereomer· $R_f = 0.4$ (75% ethyl acetate/hexane); m.p. 140.5-142°C; ^1H NMR ($CDCl_3$) δ 6.72 (dd, J = 8.0, 2.0 Hz, 1H), 6.56 (dd, J = 8.0, 5.2 Hz, 1H), 5.36 (dddd, J = 5.2, 4.2, 2.0, 1.3 Hz, 1H), 4.55 (m, 1H), 4.32 (m, 1H), 2.87 (m, 1H), 2.51 (dd, J = 13.0, 4.2 Hz, 1H), 2.45 (dd, J = 13.0, 1.3 Hz, 1H), 2.17 (m, 1H); ^{13}C NMR δ 175.5, 166.1, 136.4, 131.5, 73.9, 65.5, 63.4, 47.8, 42.2, 34.9; FT-IR ($CHCl_3$) 3024, 1777, 1180, 1124, 1006 cm^{-1}; HRMS, m/z (M^+-CO_2) calcd for $C_{10}H_9BrO_4$ 227.9786, found 227.9779; Anal. calcd for $C_{10}H_9BrO_4$: C, 43 98; H, 3.32; Br, 29.26. Found: C, 44.07; H, 3.34; Br, 29.20.

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