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# 5-BROMO-2-PYRONE: AN EASILY PREPARED AMBIPHILIC DIENE AND A SYNTHETIC EQUIVALENT OF 2-PYRONE IN MILD, THERMAL, DIELS-ALDER CYCLOADDITIONS

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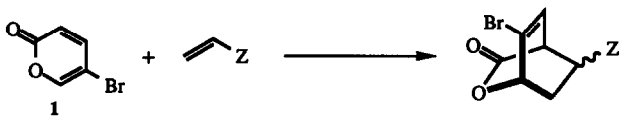
*Summary:* 5-Bromo-2-pyrone, a solid prepared easily in one-flask according to a new route (eq. 1), has been found to undergo smooth and highly regiocontrolled 2+4-cycloadditions between 25-100°C with **both** electron-poor and electron-rich dienophiles; subsequent radical debrominations produced halogen-free bicyclic lactones, including a precursor to a vitamin D steroid, thus showing 5-bromo-2-pyrone to be a practical and effective synthetic equivalent of 2-pyrone in thermal Diels-Alder cycloaddition.

Recently we discovered that 3-bromo-2-pyrone, chameleon-like, undergoes smooth and regiospecific 2 + 4-cycloadditions between 78-90°C with **both** electron-rich and electron-poor dienophiles.[2] This ambiphilic 3-bromo-2-pyrone was used in the key step for total synthesis of a new biologically active vitamin $D_3$ derivative having unexpected and important antiproliferative activity in mouse keratinocytes.[3] Now we have found that 5-bromo-2-pyrone (**1**)[4] also is an ambiphilic diene in 2+4-cycloadditions with the following advantages over its 3-bromo isomer: (1) substantially higher Diels-Alder reactivity; (2) 2 + 4-cycloadditions with a much wider range of dienophiles; and (3) easier preparation. Herein we report details of these advantages and also use of 5-bromo-2-pyrone in synthesis of A-ring synthon **5** that we have converted previously into the new antiproliferative vitamin $D_3$ analog **6**.[3]

The higher reactivity of 5- *vs.* 3-bromo-2-pyrone was established by four competition experiments. In three separate experiments, one equivalent each of 5- and 3-bromo-2-pyrone reacted at 100°C with several equivalents of methyl vinyl ketone, of methyl acrylate and of diphenyl(methyl)siloxyethylene; based on the ratios of recovered reactants as well as on the ratios of lactone bicycloadducts, 5-bromo-2-pyrone was at least six times more reactive than 3-bromo-2-pyrone. A similar competition experiment using acrylonitrile as a dienophile showed 5-bromo-2-pyrone to be at least two times more reactive than its 3-bromo isomer. This high reactivity of 5-bromo-2-pyrone (**1**) allowed unusually mild conditions to be used for successful 2 + 4-cycloadditions with **both** electron-poor and electron-rich dienophiles leading to synthetically useful, stereochemically-rich, bridged, bicyclic lactones (Scheme I).[5] The regiochemistry and the stereochemistry of these bicyclic lactones were established using 400 MHz $^1H$ NMR spectroscopy including decoupling experiments.[6] For example, the following data are typical.

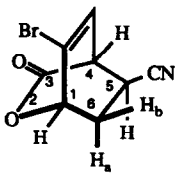
**Scheme I**



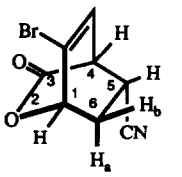
1

| Temp (°C) | Time (days) | Z | Yield (endo : exo) |
|---|---|---|---|
| 25 | 5 | $CO_2H$ | 100% (100 : 0) |
| 25 | 4 | $COCH_3$ | 89% (100 : 0)[a] |
| 100 | 2.5 | CN | 83% (54 : 46) |
| 100 | 2 | $OCH_2CH_2Cl$ | 100% (67 : 33) |
| 100 | 2 | $OSiMePh_2$ | 100% (67 : 33) |
| 100 | 2.5 | 4-$C_6H_4Br$ | 89% (80 : 20) |

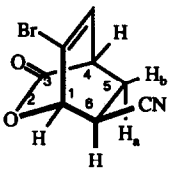
[a] 11% 6-endo was also isolated.



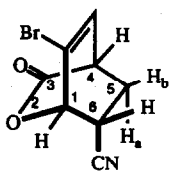
***5-endo***
$J_{1,6a}$ = 3.7 Hz; $J_{1,6b}$ = 1.5 Hz
$J_{5,6a}$ = 9.7 Hz; $J_{5,6b}$ = 3.65 Hz
$J_{4,5}$ = 2.7 Hz



***5-exo***
$J_{1,6a}$ = 3.7 Hz; $J_{1,6b}$ = 2.7 Hz
$J_{5,6a}$ = 5.4 Hz; $J_{5,6b}$ = 10.8 Hz
$J_{4,5}$ = 2.4 Hz



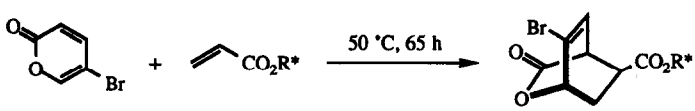
***6-endo***
$J_{1,6b}$ = 3.6 Hz
$J_{5a,6}$ = 9.5 Hz; $J_{5b,6}$ = 4.8 Hz
$J_{4,5a}$ = 2.5 Hz; $J_{4,5a}$ = 2.7 Hz



***6-exo***
$J_{1,6}$ = 1.4 Hz
$J_{5,6a}$ = 4.8 Hz; $J_{5,6b}$ = 9.5 Hz
$J_{4,5a}$ = 2.7 Hz; $J_{4,5b}$ = 2.7 Hz

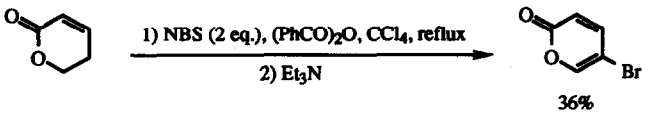
Although 3-bromo-2-pyrone was barely reactive toward *sec*-alkyl acrylate esters even at 100°C, 5-bromo-2-pyrone underwent successful cycloadditions at 50°C. Asymmetric synthesis of bicyclic lactone adducts was explored using chiral, non-racemic acrylate esters (Scheme II).[7] The best result (92.5:7.5 ratio of diastereomeric lactone 5-*endo* adducts) was achieved with *endo*-bornyl acrylate; this high level of asymmetric induction should make these bicyclic synthetic intermediates valuable chirons after removal of the chiral auxiliary.[3]

**Scheme II**



| Yield | d.e. | R* |
|---|---|---|
| 95% | 20% | PhCH(*t*-Bu)- |
| 75% | 40% | MeOOCCH(Me)- |
| 70% | 85% | *endo*-Borneol |

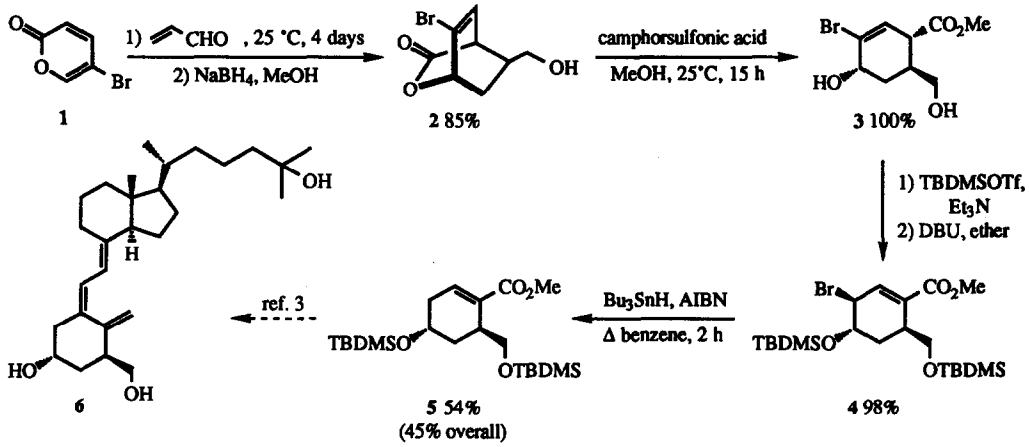
Direct, one-flask preparation of solid, 5-bromo-2-pyrone was achieved as shown in eq. 1. This bromopyrone was stable at 0°C for more than 1 year; at 25°C, gradual decomposition occurred after several weeks.[4]




(1)

5-Bromo-2-pyrone (**1**) was used also in the key cycloaddition step of a formal total synthesis of our new biologically active 1α-hydroxymethyl-25-hydroxyvitamin $D_3$ **6** (Scheme III). Room temperature atmospheric (i.e., non-high) pressure cycloaddition with acrolein followed by aldehyde reduction gave exclusively *endo*-hydroxymethyl bicyclolactone **2**.[6,9] Camphorsulfonic acid-promoted lactone methanolysis followed by alcohol protection and double bond conjugation produced cyclohexenyl bromide **4** as a single diastereomer.[5] Radical reductive debromination[8] gave regiospecifically and stereospecifically substituted cyclohexene **5** that we have converted previously into antiproliferative vitamin $D_3$ homolog **6**.[3] This scheme compares favorably with the original one (i.e. better overall yield and lower cycloaddition temperature),[3] and it illustrates for the first time that 5-bromo-3-pyrone can be used as an effective synthetic equivalent of very much less reactive 2-pyrone. Even when 2-pyrone is coaxed into cycloadditions with electron-poor dienophiles at very high pressures, the bicyclic lactone adducts are mixtures of stereoisomers,[10] in sharp contrast to the high degree of stereocontrol observed during cycloadditions of 5-bromo-2-pyrone (**1**) with α,β-unsaturated carbonyl dienophiles. Also in contrast to 5-bromo-2-pyrone, 2-pyrone itself is essentially unreactive toward electron-rich dienophiles.[6b]

**Scheme III**




In summary, easily prepared 5-bromo-2-pyrone (**1**) is a new and important addition to the increasing number of reactive and substituted 2-pyrones capable of regiospecifically and stereoselectively producing isolable, useful, highly functionalized bridged, bicyclic lactone synthetic intermediates via Diels-Alder cycloadditions under exceptionally mild conditions.[6b]

**Acknowledgment**

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## References

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3. Posner, G.H.; Nelson, T.D.; Guyton, K.Z.; Kensler, T.K. *J. Med. Chem.*, **1992**, *35*, 3280.

4. a) Pirkle, W.H.; Dines, M. *J. Org. Chem.*, **1969**, *34*, 2239; b) Bock, K.; Pedersen, C.; Rasmussen, P.; *Acta. Chem. Scand.*, **1975**, *B29*, 389; c) A mixture of 5,6-dihydropyran-2-one (0.96 g), NBS (3.56 g) and benzoyl peroxide (0.10 g) in $CCl_4$ was refluxed for several hours. After removal of solid precipitates and solvent, the amber colored gum was dissolved in $CHCl_3$ (5 mL) and $Et_3N$ (1.0 mL) was added. This dark solution was left stirring overnight. Purification by chromatography on silica gel with 15-33% ether in hexane as elutant afforded a white solid (0.65 g, 36%): m.p. 58-60°C (Lit.[4b] 60-61°C); $^1H$ NMR ($CDCl_3$) $\delta$ 6.31 (1 H, dd, $J_{3,6}$ = 1.1 Hz, $J_{3,4}$ = 9.8 Hz, H-3), 7.38 (1 H, dd, $J_{4,6}$ = 2.7 Hz, $J_{4,3}$ = 9.8 Hz, H-4), 7.62 (1 H, dd, $J_{6,3}$ = 1.1 Hz, $J_{6,4}$ = 2.7 Hz, H-6).

5. All new compounds were characterized spectroscopically and by high resolution mass spectrometry and/or by combustion analysis.

6. For details and leading references, see: a) Posner, G.H.; Nelson, T.D.; Kinter, C.M.; Johnson, N. *J. Org. Chem.*, **1992**, *57, 4083;* b) for a review see: Afarinkia, K.; Vinader, V.; Nelson, T.; Posner, G.H. *Tetrahedron*, **1992**, *48*, 9111.

7. For a review, see: Paquette, L.A. in "Asymmetric Synthesis," J.D. Morrison, Ed., Academic Press, 1984, Vol. 3, Ch. 7. See also Nougier, R.; Gras, J.-L.; Giraud, B.; Virgili, A. *Tetrahedron*, **1992**, *48*, 6245.

8. For a review, see: Neumann, W.P. *Synthesis*, **1987**, 665.

9. Typical experimental conditions are as follows: A 1 mL hydrolysis tube was charged with a magnetic stirrer bar, 5-bromo-2-pyrone (250 mg) and acrolein (0.5 mL). The contents were stirred at room temperature for 100 hours. Purification by chromatography on silica gel (50-60% ether in hexane) afforded a gummy oil: $^1H$ NMR ($CDCl_3$) $\delta$ 2.34 (1 H, ddd, $J$ = 13.9 Hz, 4.2 Hz, 1.6 Hz, H-$6_{endo}$), 2.47 (1 H, ddd, $J$ = 13.9 Hz, 9.7 Hz, 4.0 Hz, H-$6_{exo}$ ), 3.08 (1 H, ddd, $J$ = 9.7 Hz, 4.2 Hz, 2.6 Hz, H-5), 3.98 (1 H, dd, $J$ = 6.4 Hz, 2.6 Hz, 2.4 Hz, H-4), 5.23 (1 H, m, H-1), 6.52 (1 H, dd, $J$ = 6.4 Hz, 2.4 Hz, H-8), 9.56 (1 H, s, CHO). To a stirred solution of the above aldehyde in methanol (15 mL), maintained at 0°C, was added $NaBH_4$ (76 mg) over a period of 5 minutes (Caution!: Exothermic reaction! Vigorous effervescence!). Solvent was removed and the residue was taken up in methylene chloride and chromatographed directly on silica gel with ether as eluant to afford a white solid (272 mg, 85%): m.p. 78-80°C; $^1H$ NMR ($CDCl_3$) $\delta$ 1.35 (1 H, m, H-$6_{endo}$), 2.35-2.39 (2 H, m, H-5 and H-$6_{exo}$), 3.33 (1 H, dd, $J$ = 8.9 Hz, 10.7 Hz, $CH_aH_bO$), 3.56 (1 H, dd, $J$ = 6.2 Hz, 10.7 Hz, $CH_aH_bO$), 3.76 (1 H, dd, $J$ = 2.1 Hz, 6.8 Hz, H-4), 5.11 (1 H, m, H-1), 6.52 (1 H, dd, $J$ = 6.8 Hz, 2.4 Hz, H-8); $^{13}C$ NMR ($CDCl_3$) $\delta$ 29.04 (C-6), 34.95 (C-5), 44.85 (C-4), 64.11 ($CH_2O$), 80.77 (C-1), 120.8 (C-7), 128.79 (C-8), 172.18 (C-3); IR ($CHCl_3$) 3500, 1761, 994 $cm^{-1}$; MS *m/z* (EI) 233 and 235 (32, $M^+$). HRMS calcd. for $C_8H_9O_3Br$ ($M+NH_4^+$) 250.0079; Found: 250.0084.

10. a) Gladysz, J.A.; Lee, S.J.; Tomasello, J.A.V.; Yu, Y.S. *J. Org. Chem.*, **1977**, *42*, 4170; b) Pirkle, W.H.; Eckert, C.A.; Turner, W.V.; Scott, B.A.; McKendry, L.H. *ibid.*, **1976**, 2495.

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