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One step preparation of bromo-2-pyrones via bromo-decarboxylation of 2-pyrone-carboxylic acids

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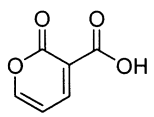
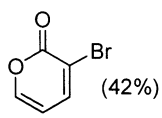
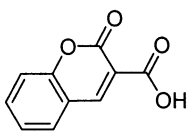
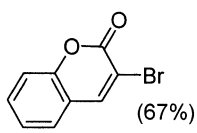
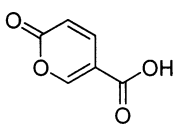
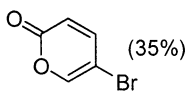
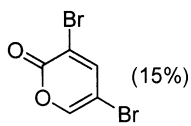
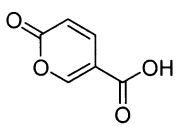
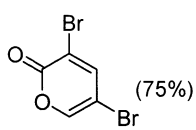
Abstract—Synthetically valuable 3-bromo-2-pyrone, 3-bromocoumarin, 5-bromo-2-pyrone, and 3,5-dibromo-2-pyrone were prepared in one step from readily available 2-pyrone-carboxylic acids via bromo-decarboxylation in good to fair yields.

Various substituted 2-pyrones[1] have been used as key synthons for the synthesis of many natural and unnatural complex molecules including taxol and a series of vitamin D_3 analogs,[2] taking advantage of their excellent stereochemical control in the Diels–Alder cycloaddition steps.[3] Brominated 2-pyrones have an additional interesting feature in that they can act as 'chameleon dienes',[3] meaning that they can react with both electron poor and rich dienophiles. As thoroughly investigated by Posner et al.,[4,5] they can undergo either normal or inverse electron-demand D-A cycloadditions, depending on the type of dienophiles being encountered, as the bromine atom at 3 or 5 position on the 2-pyrone ring can withdraw or donate electron density to the pyrone

Table 1. Hundsdiecker reactions of 2-pyrone-carboxylic acids

Entry	2-Pyrone-Carboxylic Acid	2-Pyrone-Bromide (Yield)
1		 (42%)
2		 (67%)
3		 (35%)  (15%)
3*		 (75%)

Keywords: Hundsdiecker reaction; halo-decarboxylation; Diels–Alder cycloaddition; 2-pyrones.

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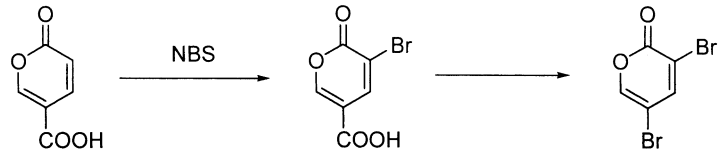


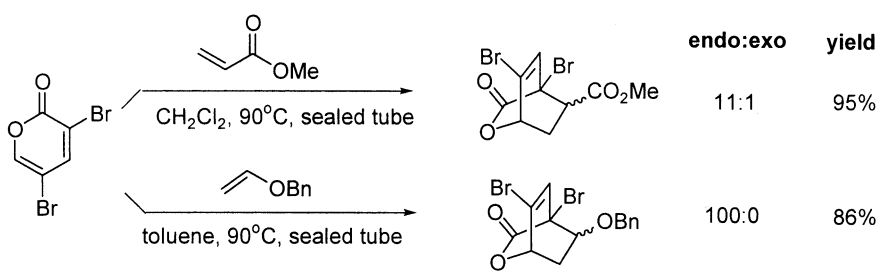
Scheme 1.

diene unit. Unfortunately, however, the versatility and usefulness of bromo-2-pyrones are much overshadowed by their difficult syntheses. For example, synthesis of 3-bromo-2-pyrone requires total three steps, starting from expensive 5,6-dihydro-2-pyrone, in an overall yield of 32%.[4a] 5-Bromo-2-pyrone is also prepared from the same starting material, either as a by-product during the synthesis of 3-bromo-2-pyrone or directly, both in less than 36% yield.[4b,c]

In the search for a more affordable and convenient way of synthesis, we undertook a systematic study on the bromo-decarboxylation of the readily available 2-pyrone-carboxylic acids. Under the conditions with metal ion catalysts or without, various aromatic and α,β-unsaturated carboxylic acids have been successfully converted to the corresponding aryl and alkenyl halides.[5] No examples on the carboxylic acids with internal ester systems were, however, reported. Jorgensen et al.[5e] reported, in fact, that coumarin-3-carboxylic acid (entry 2 in Table 1) was completely inert under their highly effective NBS/PhIO system for halodecarboxylation of α,β-unsaturated carboxylic acids.

While most of the literature methods[5] failed on our 2-pyrone system, Roy's condition[5c] using NBS and catalytic LiOAc in aqueous CH_3CN was found to be working, furnishing small amounts of the desired 3-bromo-2-pyrone from 2-pyrone-3-carboxylic acid.[3b] The reaction itself was extremely slow, thus resulting in the gradual decomposition of the product. While increasing the reaction temperature led to the decomposition of the product, excessive use of LiOAc facilitated the reaction rate. Thus, when the reaction was conducted in aqueous CH_3CN, with NBS and 1.2 equiv. of LiOAc, 2-pyrone-3-carboxylic acid was cleanly converted into 3-bromo-2-pyrone in 42% yield (entry 1), 10% better than the conventional three step method. Under the conditions, coumarin-3-carboxylic acid (entry 2) was also bromo-decarboxylated to 3-bromo-coumarin in 67% yield. Reaction on coumalic acid (entry 3) provided both 5-bromo-2-pyrone and 3,5-dibromo-2-pyrone, along with the recovered starting pyrone carboxylic acid. A series of studies were conducted to increase the product yield and, at the same time, to suppress the formation of 3,5-dibromo-2-pyrone by varying reaction conditions. Ultimately, we isolated the desired 5-bromo-2-pyrone in 35% yield, along with 3,5-dibromo-2-pyrone and the recovered starting acid in 15 and 10%, respectively, when 2 equiv. of both NBS and LiOAc were used in CH_3CN–H_2O (5:1) as a solvent after 3 days at rt. We presume that 3,5-dibromo-2-pyrone was produced from the competitive aromatic bromination at carbon 3 of the starting pyrone, followed by bromo-decarboxylation, judged from a separate control experiment that showed 5-bromo-2-pyrone did not undergo bromination at carbon 3 under the same reaction conditions (Scheme 1).

Although the yield of 5-bromo-2-pyrone here is only compatible to the literature method,[4a] our method would still be more attractive in that coumalic acid is much cheaper. Use of more than 2 equiv. of NBS to complete the reaction increased the formation of 3,5-dibromo-2-pyrone only, without much effect on 5-bromo-2-pyrone. In fact, we obtained 3,5-dibromo-2-pyrone as a main product, in an isolated yield of 75%, when 2.5 equiv. of both NBS and LiOAc were used. Noteworthy is that we now have a practical method for 3,5-dibromo-2-pyrone, which is expected to be an ambiphilic diene, similar to 3- or 5-bromo-2-pyrone. Known since 1969, 3,5-dibromo-2-pyrone has not been studied as a diene, despite the potency as an ambiphilic diene, primarily due to the intensive labor and extremely low yield in its synthesis.[4b,6] Our subsequent study showed that 3,5-dibromo-2-pyrone is indeed ambiphilic, undergoing normal and inverse electron demand D-A [4+2] cycloadditions with both methyl acrylate and benzyl vinyl ether to give rise to the highly functionalized bicyclolactones with excellent stereocontrol (Scheme 2). It turned out to be a bit more reactive and stereoselective than 3- or 5-bromo-2-pyrone. We are currently



Scheme 2.

investigating its scope and limitation as a diene through the reactions with a series of electronically and sterically distinct dienophiles.

In conclusion, we prepared synthetically useful 3-bromo-2-pyrone, 5-bromo-2-pyrone, and 3,5-dibromo-2-pyrone including 3-bromo-2-coumarine[7] in one step from readily available 2-pyrone-carboxylic acids with good to reasonable yields.

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