$P(MeNCH_2CH_2)_3N$: An Efficient Catalyst for the Synthesis of Substituted Ethyl Benzofuran-2-Carboxylates

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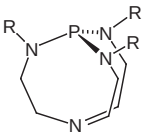
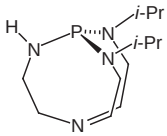
Abstract: A superior method for the synthesis of substituted ethyl benzofuran-2-carboxylates in 80-99% yields from substituted 2-formylphenoxy ethylcarboxylates using 0.4 equiv of commercially available $P(MeNCH_2CH_2)_3N$ at 70 °C for 3 hours is described.

Key words: benzofurans, bicyclic compounds, catalysis, cyclizations, heterocyclics



1a, R = Me
1b, R = *i*-Pr



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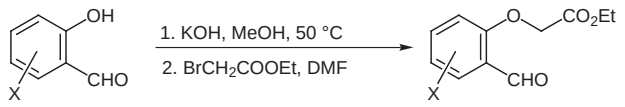
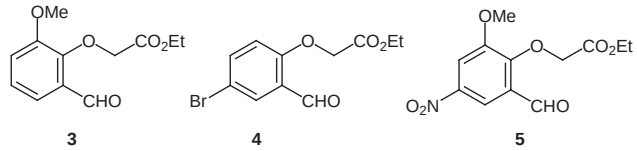
The benzofuran moiety is encountered in the synthesis of fluorogenic reagents,[1] CNS depressants,[2] bacteriostatic agents,[3] inflammation inhibitors,[4] angiotensin II type I receptor antagonists,[5] antitumor antibiotics[6] and analgesic agents.[7] Although a variety of methods for the synthesis of 2-(4-substituted phenyl)benzofurans[1,8] have been developed, the synthesis of ethyl benzofuran-2-carboxylates has been problematic. A major difficulty encountered in the synthesis of ethyl benzofuran-2-carboxylate is the hydrolysis of the ester functionality and the Cannizarro reaction that occurs when using potassium hydroxide as a base.[9] The problem of ester hydrolysis was solved by using sodium ethoxide as a base, which gave the intermediate hydroxy-2,3-dihydrofuran. Dehydration of hydroxy-2,3-dihydrofuran was achieved using sulfuric acid, thereby making this approach indirect.[5] Recently, Patel et al. reported that the best method to synthesize ethyl 7-methoxy-5-nitrobenzofuran-2-carboxylate (44% yield) from ethyl 2-(6-formyl-2-methoxy-4-nitrophenoxy)acetate is to use DBU as a base in refluxing ethanol.[6]

We have recently developed efficient methods for the synthesis of esters,[10] benzyl ethers,[11] β-hydroxynitriles,[12] a chiral fluorescent auxiliary,[13] alkenes (via dehydrohalogenation),[14] pyrroles,[15] oxazoles,[15] porphyrins,[15] C-acyl-α-amino acid esters,[15] C-alkyl esters[16] and *trans* epoxides[17] using the commercially available compound **1a** or its derivative **1b** as a stoichiometric base. Using the catalytic properties of **1a**, superior methods for the synthesis of isocyanurates,[18] silyl ethers,[19,20] oxazolines,[21] and β-methoxy ketones[22] have been developed. Both **1a** and **2** are excellent catalysts for the synthesis of glutaronitriles,[23] β-hydroxynitriles[12] and α,β-unsaturated nitriles.[24]

Herein we report an efficient and direct synthetic route to a variety of functionalized ethyl benzofuran-2-carboxylates using **1a** as a catalyst in refluxing ethanol. To the best of our knowledge, this is the first example for the use of a nonionic base as a catalyst to synthesize benzofuran derivatives. Commercially available (2-formylphenoxy)ethanoates were alkylated in 80-95% yield using a literature procedure[6] which was modified to make it general for substrates **3**-**6**.





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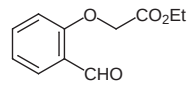

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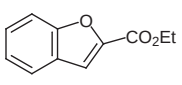

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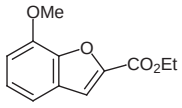

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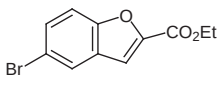

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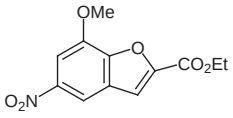

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The intramolecular aldol cyclization of substrates **3**-**6**, followed by subsequent dehydration of the intermediate hydroxy dihydrofuran was achieved using **1a** as a catalyst in ethanol at 70 °C for 3 hours (Table). The superiority of **1a** over other typically employed bases was also demonstrated. Thus, reaction of 1.0 mmol of **6** in 1 mL of THF at 67 °C for 3 hours in the presence of 0.4 mmol of the indicated catalyst provided the following yields of **7** (cf. chromatographic separation conditions in the Table):

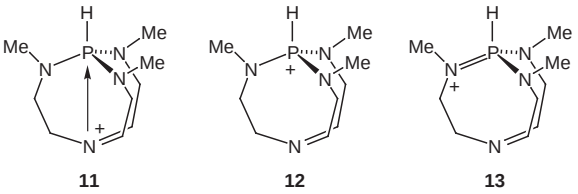
1,8-diazabicyclo[5.3.0]undec-7-ene (DBU), 60%; 4-dimethylaminopyridine (DMAP), 0%; diazabicyclo[2.2.2]octane, 0%; **1a**, 98%; sodium ethoxide, 0%; di-*iso*-propylethylamine, 0%. The yield of **7** in a variety of solvents such as THF, trifluorotoluene and ethanol using 0.4 equivalents of **1a** at 70 °C for 3 hours was >98%. It should be noted that trifluorotoluene (bp 102 °C) is a substitute for methylene chloride (suspected carcinogen) and related solvents, not only because of recent regulations enforced by OSHA but also because of its compatibility with a wide variety of organic reactions.[25] When **5** was refluxed in dioxane with 3 equivalents of potassium hydroxide, only 1% of **10** was obtained.[9] Recently, Patel and coworkers reported that they tried several methods (unspecified) to synthesize **10** from **5** and that the best method utilized 1.1 equivalents of DBU as a base in refluxing ethanol to give the product in only 44% yield.[6] By contrast, our method gave the product in 80% yield using only 0.4 equivalents of **1a**. Whereas compound **9** was prepared from **4** using 1.1 equivalents of NaOEt in refluxing ethanol to give the hydroxy dihydrofuran (which was subsequently dehydrated with concentrated sulfuric acid to give the desired product in 55% overall yield[5]) our method gave a 98% yield of the product using 40 mol% of **1a** at 70 °C in 3 hours.

Table Synthesis of Substituted Benzofurans Using 0.4 equivalents of **1a** in Ethanol at 70 °C for 3 h

aldehyde	eluent ratio[a]	product	% yield
3	7:3	**8**	98
4	7:3	**9**	98
5	1:1	**10**	80
6	7:3	**7**	99

[a] Hexanes:ethyl acetate.

The pathway for the formation of the benzofurans is assumed to proceed via deprotonation of the methylene group by EtO$^-$ formed as a result of the deprotonation of EtOH by **1a**. The enolate thus produced undergoes C-C bond formation to form an alkoxide that abstracts a proton from the solvent to forma a β-hydroxy ester. The β-hydroxy ester finally undergoes base-assisted thermal dehydration. The unusually strong basicity of **1a** is associated with the formation of three stable five-membered rings in the corresponding conjugate acid after proton abstraction from a substrate. We have already documented that **1a** is capable of deprotonating primary alcohols.[17] We believe that the extensive delocalization of the positive charge (as indicated in structures **11**, **12** and the three resonance structures implied in **13**) in the bulky cation **11** enhances the reactivity of the weakly bound ion pairs compared with the strongly bound ion pairs formed from ionic bases. The low charge density on cation **11** probably prevents it from activating the carbonyl group of the ester (for base hydrolysis) and the aldehyde functionality (for the Cannizarro reaction). It should be noted that **1a** is in equilibrium with 1 equivalent of water in CD_3CN with the ratio of **1a**:**11**(OH) being 4:1. This equilibrium was shifted to the right by adding excess water.[26] Interestingly, a tetraalkylammonium isopropoxide has been used to alkylate aldehydes directly,[27] although the reaction studied by these authors was not a condensation per se as in our experiments.



11 **12** **13**

Ethanol, trifluorotoluene, tetrahydrofuran, acetonitrile, dimethyl formamide, methanol, salicylaldehyde, ethyl bromoacetate, *o*-vanillin and 5-bromo salicylaldehyde (Aldrich Chemical Co.) were used as received. 2-Hydroxy-3-methoxy-5-nitrobenzaldehyde (Lancaster Chemical Co.) was used as received. All reactions were carried out under N_2. Although the nonionic base **1a** is commercially available (Strem), we prepared it according to our previously published method[28] and stored it under N_2.

General procedure for the preparation of 3-6

In a round-bottomed flask fitted with a thermometer, a reflux condenser and a nitrogen inlet, was added 50 mL of methanol followed by the addition of 0.3 g (6 mmol) of finely powdered potassium hydroxide. To this stirred suspension was added 5 mmol of the aldehyde. The reaction mixture was heated to 50 °C for 30 min and then concentrated to dryness under vacuum. After the addition of DMF (50 mL) to the solid, the reaction mixture was stirred for 5 min and then it was cooled to 0 °C. To this was added 1.0 mL of ethyl bromoacetate followed by allowing the reaction mixture to warm up to 25 °C overnight. Removal of the DMF was carried out under vacuum at 50 °C. To the solid residue was added 20 mL of water followed by the addition of 25 mL of ethyl acetate. After stirring for 15 min the layers were separated. The aqueous layer was extracted with 2 × 25 mL of ethyl acetate. The combined organic layer was washed with 25 mL of water and then with saturated brine. The organic layer was dried over magnesium sulfate and concentrated to give the crude product which was purified by silica gel column chromatography using the gradient elution technique. After the column was loaded with the crude product, the polarity of the solvent was increased in steps of 5% using 50 mL of eluent in each step, starting from 50 mL of 100% hexanes and ending with the ratio indicated in the Table. The fractions containing the product were concentrated under vacuum to give the product that was found to be >98% pure by ^{1}H NMR analysis.

General procedure for the preparation of 7-10

In a test tube containing a magnetic stir bar was placed 1 mL of ethanol and 0.4 mmol (86 mg) of **1a** under nitrogen. To this homogeneous solution was added 1 mmol of the substrate. The reaction mixture was stirred under nitrogen at 70 °C for 3 h. The crude product was purified by silica gel column chromatography using the gradient elution technique. Thus, after the column was loaded with the crude product, the polarity of the solvent was increased in steps of 5% using 50 mL of eluent in each step, starting from 50 mL of 100% hexanes and ending with the ratio indicated in the Table. The fractions containing the desired compound were concentrated under vacuum to give the product, which was found to be >98% pure by ^{1}H NMR analysis.

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