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Synthesis of substituted benzofuran-3-ylacetic acids based on three-component condensation of polyalkoxyphenols, arylglyoxals and Meldrum's acid

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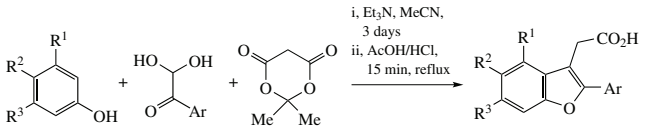
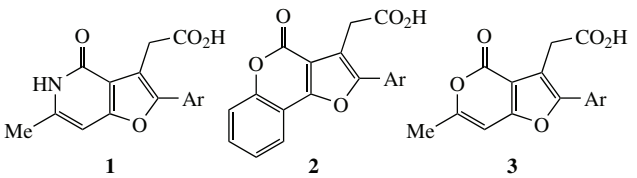
Substituted benzofuran-3-ylacetic acids were obtained by three-component condensation of polyalkoxyphenols, arylglyoxals and Meldrum's acid.



Benzofuran derivatives have a broad spectrum of biological activity and can be applied as melatonin receptor inhibitors,[1] antifungal,[2] antitumor,[3,4] antimicrobial and antioxidant agents.[5] Substituted benzofurans are proposed to be used as cholinesterase inhibitors for the treatment of Alzheimer's disease.[6] Moreover, PPARδ agonists for the treatment of metabolic syndrome were synthesized on the basis of benzofurylacetic acids.[7] Therefore, to search for new syntheses of benzofuran derivatives is of importance. The effective technique for this goal is to employ multicomponent reaction concept which allows one to avoid a complex sequence of multistage synthesis.[8,9]

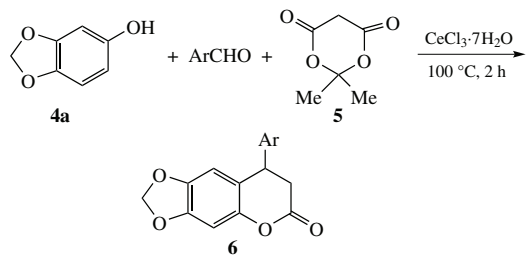
Earlier, we have studied multicomponent reactions with participation of arylglyoxals, heterocyclic enols and Meldrum's acid[10] and obtained fused heterocyclic acids **1**–**3**. The procedure comprised the heating of the reactant mixture in acetonitrile in the presence of triethylamine followed by acid treatment.



1 **2** **3**

On the other hand, the reaction between 3,4-methylendioxyphenol **4a**, aromatic aldehydes and Meldrum's acid **5** leading to products of type **6** was reported[11] (Scheme 1). Based on these data, one may assume that multicomponent reactions of arylglyoxals, polyalkoxyphenols and Meldrum's acid would provide an access to related benzofuran-3-ylacetic acids.

The aim of this study was elaboration of new procedure for the synthesis of benzofuran-3-ylacetic acids using multicomponent condensation polyalkoxyphenols **4a**–**c** with Meldrum's acid **5** and arylglyoxals **7a**–**g** (Scheme 2). In fact, this reaction performed in acetonitrile in the presence of triethylamine and subsequent treatment with hydrochloric and acetic acids afforded the target products **8a**–**o**. It should be noted that as in



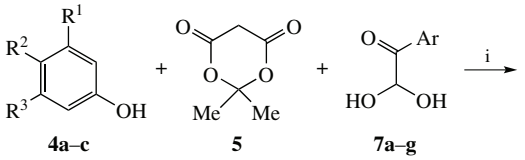
4a **5** **6**

Scheme 1

the case of heterocyclic enols[10] the investigated reaction proceeds in two stages, the first one giving intermediate dihydrocoumarins **A**. At the final stage, the acid-assisted recyclization occurs leading thus to target benzofuran-3-ylacetic acids **8a**–**o** (see Scheme 2).

The distinctive feature of the studied procedure is milder reaction conditions, namely, the continuous keeping the reactant solution in acetonitrile at room temperature. Apparently, this becomes possible due to higher electron-donating properties of polyalkoxyphenols as compared to the previously described heterocyclic enols.[10] Attempts to accelerate the reaction by heating causes tarring of the reaction mass, and the target products are not obtained. The procedure herein developed can be applicable only for phenols with several electron-donating substituents in aromatic ring. Our attempts to prepare similar benzofuran-3-ylacetic acids from less electron-rich phenol, its alkyl, halo and monoalkoxy derivatives were not successful even upon heating the reaction mixture. The synthesized acids **8a**–**o** are solids, their structure was confirmed by NMR spectroscopy and high-resolution mass spectrometry. The ^{1}H NMR spectra contained characteristic signals of proton for methylene fragment at 3.75–3.93 ppm.

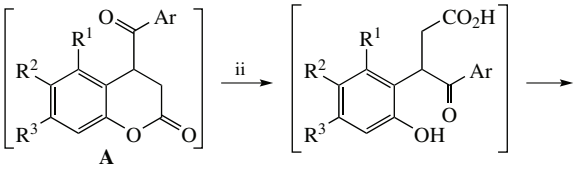
In summary, we developed a simple and effective procedure for the synthesis of substituted benzofuran-3-ylacetic acids **8a**–**o** based on multicomponent condensation of polyalkoxyphenols **4a**–**c**, Meldrum's acid **5** and arylglyoxals **7a**–**g**. The presented



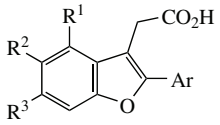
4a–c **5** **7a–g**

4a R^1 = H, $R^2 + R^3 = OCH_2O$
4b R^1 = H, $R^2 = R^3$ = OMe
4c $R^1 = R^2 = R^3$ = OMe

7a Ar = Ph
7b Ar = 4-MeC_6H_4
7c Ar = 4-$MeOC_6H_4$
7d Ar = 4-ClC_6H_4
7e Ar = 4-BrC_6H_4
7f Ar = 1,3-benzodioxol-5-yl
7g Ar = 6-methoxynaphthalen-2-yl



A



8a–o

8	R^1	R^2	R^3	Ar	Yield (%)
a	H	OMe	OMe	Ph	69
b	H	OCH_2O		Ph	55
c	H	OCH_2O		4-MeC_6H_4	53
d	H	OMe	OMe	4-MeC_6H_4	64
e	H	OMe	OMe	4-$MeOC_6H_4$	61
f	OMe	OMe	OMe	4-$MeOC_6H_4$	45
g	H	OCH_2O		4-$MeOC_6H_4$	70
h	H	OMe	OMe	4-ClC_6H_4	57
i	H	OCH_2O		4-ClC_6H_4	60
j	H	OCH_2O		4-BrC_6H_4	62
k	H	OMe	OMe	1,3-benzodioxol-5-yl	53
l	H	OCH_2O		1,3-benzodioxol-5-yl	69
m	H	OMe	OMe	6-methoxynaphthalen-2-yl	55
n	H	OCH_2O		6-methoxynaphthalen-2-yl	62
o	OMe	OMe	OMe	Ph	47

Scheme 2 *Reagents and conditions*: i, Et_3N, MeCN, 3 days; ii, HCl/AcOH, reflux, 15 min.

approach can be used for the preparation of fused furylacetic acids based on various electron-rich phenols of synthetic and natural origin.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.09.037.

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