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Short communication

SHORT COMMUNICATION

N-Methylimidazole-mediated synthesis of aryl alkyl ethers under microwave irradiation and solvent free conditions

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Abstract: A microwave-assisted three-component reaction was established for the synthesis of aryl alkyl ethers. The reaction was performed under solvent--free conditions in the presence of *N*-methylimidazole and dialkyl acetylenedicarboxylate to furnish a novel approach to *O*-alkylation of phenol derivatives in high yield.

Keywords: microwave-assisted; three-component reaction; *N*-methylimidazole; *O*-alkylation; dialkyl acetylenedicarboxylate.

INTRODUCTION

Aryl ethers are used as raw materials for the manufacture of a variety of durable surface coatings, paints, varnishes, printing inks, wire enamels, surface-active agents, rubber chemicals, antioxidants, fungicides, heat carriers, foaming agents, synthetic resins and perfumes.[1–4] These compounds can be prepared by different approaches.

It was found that alkylation of phenol could be performed with homogenous catalytic systems, such as imidazolium salts ionic liquids,[5] use of bases such as NaOH and K_2CO_3 in the presence of dimethyl sulfate (DMSA) catalyzed by solid base zeolites,[6] Cs-loaded zeolites,[7] dimethyl carbonate under solid/liquid phase transfer systems[8] and KNO_3/NaY.[9] Though high catalytic performances were achieved in homogenous systems, the drawbacks were poor catalyst recovery and product separation. Hence, some heterogeneous catalysts for the selective synthesis of aryl alkyl ether were investigated.[10] Basic zeolites, alumina or alumina–silica were usually used as catalysts for the vapor phase alkylation of

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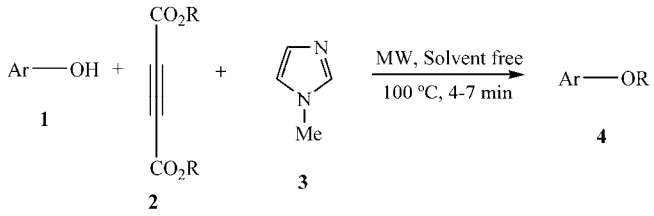
phenol,[11] but considerable amounts of by-products (*C*-alkylation) were always present.

Thus, the development of an efficient, safe, and environmentally friendly method for *O*-alkylation constitutes an important challenge; moreover, synthesis without solvents under microwave irradiation offers several advantages. The absence of solvent may reduce the risk of hazardous explosions when the reaction occurs in a closed vessel in an oven.[12,13] The addition of phenol derivatives to *tert*-butyl propiolate in the presence of triphenylphosphine, which led to alkyl aryloxypropenoates, in CH_2Cl_2 at room temperature was previously described.[3] In connection with ongoing work on the development of new synthetic methods to heterocyclic compounds using phenol derivatives,[14,15] herein, a method to realize *O*-alkylation of some OH acids by nucleophilic substitution reactions (Scheme 1) is reported.



1	Ar
a	4-hydroxycoumarin
b	7-hydroxycoumarin
c	4-hydroxyquinoline
d	6-hydroxyquinoline
e	8-hydroxyquinoline
f	2-naphthol

2	R
a	Me
b	Et
c	^{t}Bu

4	Ar	R	Yield %
a=c	4-hydroxycoumarin	Me	95
b	4-hydroxycoumarin	Et	90
d=f	7-hydroxycoumarin	Me	98
e	7-hydroxycoumarin	Et	95
g	4-hydroxyquinoline	Me	85
h	6-hydroxyquinoline	Me	85
i=j	8-hydroxyquinoline	Me	95
k	2-naphthol	Me	90

Scheme 1. Typical procedure for the preparation of compounds **4a**–**k**.

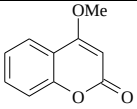
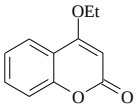
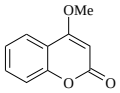
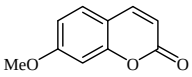
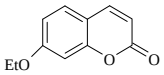
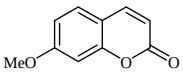
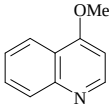
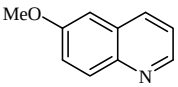
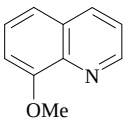
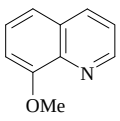
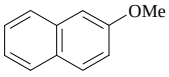
RESULTS AND DISCUSSION

Our studies were initiated by the reaction of 4-hydroxycoumarin (**1a**) with dimethyl acetylenedicarboxylate (DMAD) (**2a**) or diethyl acetylenedicarboxylate (DEAD) (**2b**) in the presence of *N*-methylimidazole (**3**) without solvent under microwave irradiation (green chemistry), which afforded the 4-alkoxy coumarins **4a** and **b**, respectively, in high yields after 4–7 min.

Surprisingly, when this reaction was performed with di-*tert*-butyl acetylenedicarboxylate (DTAD, **2c**), TLC and the ^{1}H-NMR spectrum of the product showed that the obtained product was 4-methoxycoumarin (**4a**). Then the substrate scope of this reaction was investigated by using hydroxyquinoline deri-

vatives and naphthols under the same conditions. As expected, using DMAD and DEAD, the products were methoxy and ethoxy derivatives, respectively. When the reaction occurred with DTAD, the isolated products were methoxy derivatives. The structures, yields and melting points of the products are summarized in Table I.

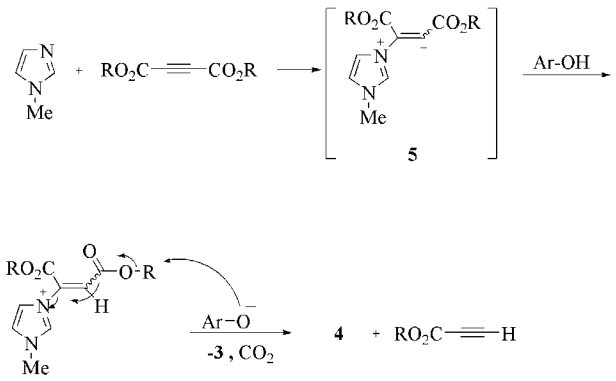
TABLE I. *O*-Alkylation of hydroxycoumarins, hydroxyquinolines and 2-naphthol

Entry	Ar	R	Product	Time, min	Yield, %
1	4-Hydroxycoumarin	Me		6	95
2	4-Hydroxycoumarin	Et		7	90
3	4-Hydroxycoumarin	*t*-Bu		5	80
4	7-Hydroxycoumarin	Me		4	98
5	7-Hydroxycoumarin	Et		4	95
6	7-Hydroxycoumarin	*t*-Bu		5	70
7	4-Hydroxyquinoline	Me		7	85
8	6-Hydroxyquinoline	Me		6	85
9	8-Hydroxyquinoline	Me		7	95
10	8-Hydroxyquinoline	*t*-Bu		7	85
11	2-Naphthol	Me		7	90

To illustrate the role of *N*-methylimidazole (**3**), the reaction of 2-naphthol with DMAD was studied in the absence of *N*-methylimidazole. The formation of

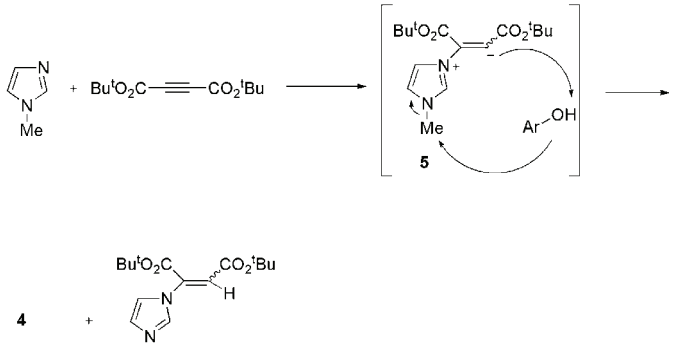
the *O*-methylated product was not observed in the absence of *N*-methylimidazole. The TLC and ^{1}H-NMR spectra of the reaction mixture confirmed only 2-naphthol.

It is reasonable to assume that the products **4a**, **b**, **d**, **e**, **g**–**i** and **k** result from initial addition of *N*-methylimidazole to the dialkyl acetylenedicarboxylates **2a** and **b** and subsequent protonation of the zwitterions **5** by OH acids.[16] Then the reactions proceed *via* a protonated intermediate that activates the electrophile for attack by the conjugate base of phenol onto the carbon atom group of the acetylenic ester, which provides the stable products (Scheme 2). The fact that DMAD and DEAD reacted showed that the displacement step could have S_N2 character.[17]



Scheme 2. A possible mechanism for the preparation of **4a**, **b**, **d**, **e**, **g**–**i** and **k**.

Formation of the product **4c**, **4f** and **4j** using DTAD suggests that steric effects are important and hence, the conjugate base of phenol attacks into the methyl group of *N*-methylimidazole instead of the alkyl group of the acetylenic ester, which again suggests that the displacement step could have S_N2 character (Scheme 3).



Scheme 3. A possible mechanism for reactions of DTAD.

EXPERIMENTAL

Microwave irradiation was performed with a Milestone ETHOS 1600 microwave oven. The chemicals were purchased from Fluka and used without further purification. The melting points were measured on an Electrothermal 9100 apparatus. The IR spectra were recorded on a Shimadzu IR-460 spectrometer. The ^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker Avance DRX-400 spectrometer using $CDCl_3$ as the applied solvent and TMS as an internal standard.

Physical, analytical and spectral data for the compounds **4a**–**k** are given in the Supplementary material to this paper.

*Typical procedure for the synthesis of alkoxycoumarin (**4**)*

In a 10-mL reaction vial, a mixture of *N*-methylimidazole (**3**, 0.26 g, 2.0 mmol) and dimethyl acetylenedicarboxylate (**2a**, 0.24 mL, 2.0 mmol) under solvent-free condition was stirred for 1 min. Subsequently, 4-hydroxycoumarin (**1a**, 0.32 g, 2.0 mmol) was added to the reaction mixture, and the reaction vial was capped and pre-stirred for 20 s. The mixture was subjected to microwave irradiation at a power of 600 W for 6 min at 100 °C. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature. The resulting precipitate was separated by filtration and recrystallized from diethyl ether (Et_2O) to afford the pure compound **4a**.

CONCLUSIONS

In the present investigation, a simple and economical one-step procedure for ethers of coumarin, quinoline and naphthol under microwave irradiation was developed. This method offers marked improvements concerning high isolated yields of the products, avoidance of hazardous organic solvents and toxic catalysts and a simple protocol of the alkylation of different phenols.

SUPPLEMENTARY MATERIAL

Physical, analytical and spectral data for the compounds **4a**–**k** are available electronically from http://www.shd.org.rs/JSCS/, or from the corresponding author on request.

ИЗВОД

СИНТЕЗА АЛКИЛ-АРИЛ-ЕТАРА У ПРИСУСТВУ *N*-МЕТИЛИМИДАЗОЛА ПОД УТИЦАЈЕМ МИКРОТАЛАСА И У ОДСУСТВУ РАСТВАРАЧА

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Развијен је поступак за трокомпонентну реакцију за синтезу арил-алкил-етара под утицајем микроталаса. Реакције су вршене у присуству *N*-метилимидазола и диалкил ацетилендикарбоксилата без растварача. Овим поступком је остварена синтеза *O*-алкилованих фенола у високом приносу.

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