

FOUR-COMPONENT AND ONE-POT REACTION BETWEEN MELDRUM'S ACID, ARYL ALDEHYDES AND ISOCYANIDES IN THE PRESENCE OF PRIMARY AMINES UNDER SOLVENT-FREE CONDITIONS

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ABSTRACT

An improved four-component reaction of isocyanides is described. The reaction between Meldrum's acid, aryl aldehydes with isocyanides in the presence of two equivalents primary amines under solvent-free conditions at room temperature leads to triamides derivatives in good yields.

Keywords: *Four-component Reaction, Meldrum's Acid, Isocyanides, Aryl Aldehydes, Primary Amines, Triamides Derivatives*

INTRODUCTION

Modern synthetic design demands high efficiency in terms of minimization of synthetic steps together with maximization of complexity (Trost, 1991). One of the ways to fulfill these goals is the development and use of multicomponent reactions which consist of several simultaneous bond-forming reactions and allow the high efficient synthesis of complex molecules starting from simple substrates in a one-pot manner (Bienayme *et al.*, 2000; Wangelin *et al.*, 2003; Orru *et al.*, 2003). An important subject that attracted a great deal of attention from organic and bioorganic chemists during the last few decades has been the developing of new strategies for the synthesis of complex molecular structures from easily available substrates by short and effective routs.

The most important of these strategies has been the developing of multi-component reactions (MCRs), a reaction in which three or more compounds connect together by covalent bonds to produce a complex molecule contains the main structure of all the starting materials. As MCRs are one-pot reactions, they are easier to carry out than multistep syntheses.

Coupled with high-throughput library screening, this strategy was an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds (Eilbracht *et al.*, 1999; Ugi, 2001; Bagley *et al.*, 2002; Bora *et al.*, 2003; Weber, 2002). Among the MCRs, isocyanide based multi-component reactions (IMCRs) have gained the most attention by the organic chemists.

Ugi four component reaction(U-4CR) (Ugi *et al.*, 2003; Domling, 2000; Domling *et al.*, 2006) and Passerini three component reaction (P-3CR) (Passerini, 1921) are among the most important IMCRs. U-4CR and P-3CR describe the reaction of isocyanides with carboxylic acids in the presence of imines or aldehydes, respectively.

In the context of our recent studies (Yavari *et al.*, 2003) on the reactivity of isopropylidene Meldrum's acid, we studied the reaction between Meldrum's acid, aryl aldehydes with isocyanides in the presence of two equivalents primary amines under solvent-free conditions at room temperature.

MATERIALS AND METHODS

Melting points were determined with an Electrothermal 9100 apparatus. Elemental analyses were performed using a Heraeus CHN–O–Rapid analyser. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ¹H and ¹³C spectra were recorded on Bruker DRX-400 Avance spectrometer in CDCl₃ using TMS as the internal standard. Chemicals were purchased from Fluka (Buchs, Switzerland) and were used without further purification.

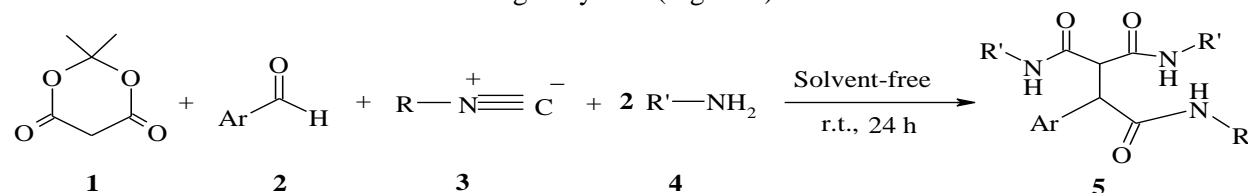
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General Procedure

To Meldrum's acid (1 mmol) at r.t. was added aryl aldehyde (1 mmol). The reaction mixture was stirred for 5 min. Then, primary amine (2 mmol) was added at this temperature. Reaction mixture was then stirred for one minute. isocyanide (1 mmol) was added and the reaction mixture was stirred for more 24h at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, The resulting precipitate was collected and washed with 5 ml of cold diethyl ether to afford the pure title compounds.

RESULTS AND DISCUSSION

The reaction of Meldrum's acid **1** and aryl aldehydes **2** with isocyanides **3** in the presence of primary amines **4** leads to triamides derivatives **5** in good yields (Figure 1).



5	Ar	R	R'	Yield%*
a	4-NO ₂ -C ₆ H ₄	t-Bu	Phenyl	90
b	4-NO ₂ -C ₆ H ₄	Cy	Phenyl	85
c	4-NO ₂ -C ₆ H ₄	t-Bu	1-Naphthyl	80
d	4-NO ₂ -C ₆ H ₄	Cy	1-Naphthyl	85
e	4-Br-C ₆ H ₄	Cy	Phenyl	89

* Isolated yields

Figure 1: Four-component reaction between Meldrum's acid, aryl aldehydes and isocyanides in the presence of primary amines under solvent-free conditions

To study the scope of the reaction, a series of aromatic aldehydes, isocyanides and primary amines in the presence of Meldrum's acid under solvent-free conditions at room temperature were examined. The results are shown in Table 1.

Table 1: Reaction between Meldrum's acid, aryl aldehydes with isocyanides in the presence of primary amines under solvent-free conditions at room temperature

Entry	Product	Time(h)	Yield%	mp (°C)	
				found	reported
1	5a	24	90	297-300	300-301
2	5b	24	85	300-302	304-305
3	5c	24	80	292-294	290-291
4	5d	24	85	288-290	289-290
5	5e	24	89	324-326	327-329

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The compounds **5a-e** was characterized by their ¹H-NMR and IR spectroscopy and elemental analyses. Spectral data were compared with the literature data (Shaabani *et al.*, 2003). The mechanism of the reaction is probably similar to that published by Shaabani *et al.*, (2003).

Conclusion

In summary, We now report the four-component reaction between Meldrum's acid, aryl aldehydes and isocyanides in the presence of primary amines under solvent-free conditions to afford triamides derivatives in good yields. The present method does not involve any hazardous organic solvent. Therefore, this procedure could be classified as green chemistry.

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