



An improved microwave assisted protocol for Yonemitsu-type trimolecular condensation



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ABSTRACT

Due to the presence of the indole ring in a number of bioactive compounds, novel methods for the preparation of polyfunctionalized indole derivatives are of great interest. The combined use of Lewis acid catalysis and microwave irradiation furnished satisfactory results in the Yonemitsu-type trimolecular condensation of indoles with aldehydes and 1,3-dicarbonyl compounds, such as malonates and acetoacetates.

The main advantage of this procedure is the use of a catalytic amount of the Lewis acid and reduction in reaction time. The one pot procedure avoids the isolation and purification of intermediates, thus making the process more environmentally sustainable. The protocol has also been successfully applied to the preparation of novel indole-coumarin derivatives of potential biological interest.

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1. Introduction

The development of solutions for efficient and economical multiple bond-forming transformations is an important goal for sustainable chemistry development.¹ In a recent perspective paper, members of the American Chemical Society's Green Chemistry Roundtable emphasized the fundamental importance of considering the potential time, energy, and solvent savings afforded by 'telescoping' synthesis. Collapsing a multistep process into a smaller number of operations will soon become necessary to move toward more environmentally sustainable processes.²

In this field, fast and high yielding processes for the synthesis of 3-substituted indoles have been deeply investigated since tryptophan, tryptamine, and other indole derivatives are present in a number of bioactive natural compounds,³ pharmaceutical products,⁴ agrochemicals,⁵ and functional materials.⁶ β -Alkyl-tryptophans in particular have been recently deeply studied for the conformational properties they induce in peptide fragments and for the effect that this secondary structures have on the bioactivity of small peptides.⁷

The trimolecular condensation of indole with Meldrum's acid and an aldehyde, first reported by Yonemitsu and co-workers in the late seventies,⁸ facilitates the synthesis of 3-substituted indoles. Recently, Sapi and co-workers,⁹ efficiently applied this reaction to

the diastereoselective synthesis of chiral derivatives from sugar-derived aldehydes in the presence of proline as catalyst. This MCR (multicomponent reaction) has been reinvestigated in order to overcome its limitations. Under the standard conditions, poor results were obtained when Meldrum's acid was replaced with other active methylene compounds, probably due to the difference in pK_a values. This MCR may be considered to be a one-pot two steps process (Fig. 1), since the first Knöevenagel condensation between Meldrum's acid and aldehyde (step 1) is followed by the Michael addition of indole to the alkylidene malonate intermediate (step 2).

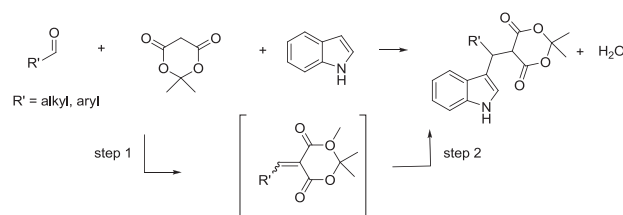


Fig. 1. Steps of the Yonemitsu multicomponent reaction.

Additives and catalysts able to activate both steps have been introduced to promote the reaction. Recently Fontana and co-workers¹⁰ successfully performed a Yonemitsu-type reactions with 1,3-dicarbonyl compounds using Ti(IV) derivatives and triethylamine to promote trimolecular condensations. Their procedure allowed the isolation in excellent yields of the compounds derived

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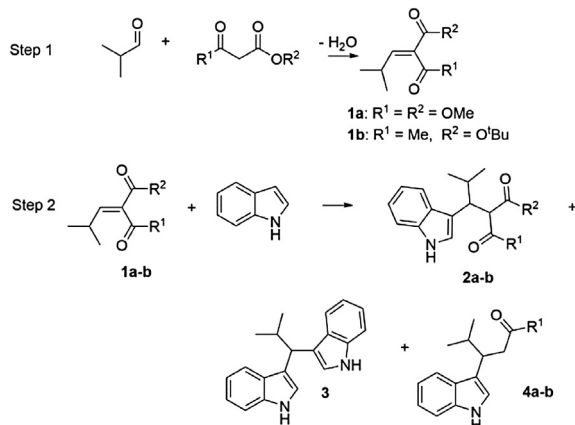
from malonates, while the reaction involving acetoacetates afforded the desired compounds in 40–50% yields, together with products due to further condensation. The synthetic protocol always required the use of stoichiometric amounts of TiCl_4 or $\text{TiCl}_2(\text{O}i\text{-Pr})_2$ and triethylamine. In a recent paper, Curini and co-workers¹¹ reported their results in the condensation of indole with aldehyde and dimethyl malonate in the presence of catalytic $\text{Yb}(\text{OTf})_3$, by promoting the reaction with ultrasonication for 12 h. The main drawbacks of this procedure are the long reaction times as well as the unsatisfactory yields.

The use of microwave heating to increase reaction rate, while reducing side products in multicomponent reactions, has been deeply investigated in the last 15 years.¹² Recently, our research group has been interested in enhancing reaction efficiency by means of MAOS (microwave assisted organic synthesis). In particular, we have applied this technology to the Knoevenagel reaction between 1,3-dicarbonyl compounds and aldehydes to afford building blocks for bioactive compounds preparation.¹³

2. Results and discussion

On the basis of this expertise, we decided to explore the effect of microwaves on Yonemitsu-type multicomponent reactions, to verify the possibility of overcoming the need to use stoichiometric amount of catalyst or a very long reaction times.

To optimize conditions, we chose as standard reaction the condensation of dimethyl malonate with isobutanal and indole (Scheme 1). As a first approach, we tried to perform a domino MCR by adding all the reagents simultaneously in the microwave reactor and irradiating the neat mixture at 250 W for 20 min. Under these conditions several products were observed in the crude ^1H NMR spectra, which is likely because a number of condensations among the reagents can occur, therefore we decided to optimize the reaction by searching the best conditions for each step. The first step had been already optimized and reported in previous papers.¹¹ By submitting equimolar amounts of dimethyl malonate or acetoacetate and isobutanal in the presence of 15% of piperidine to microwave irradiation at 250 W for 7 min, alkylidene malonate **1a** or alkylidene acetoacetate **1b** were isolated in 90% yield after flash chromatography. We then focused our attention on the second step that was initially performed on purified **1a**. The conjugate addition of indole to alkylidene malonate has been deeply explored and many successful examples of Lewis acid catalyzed diastereo- and enantioselective reactions have been reported in the literature¹⁴ but, to our knowledge, no microwave catalyzed procedure has been developed. The reaction was tested under different conditions, by changing catalyst, irradiation power, solvent, and times. Selected results are reported in Table 1.



Scheme 1. Steps of the condensation among isobutanal, dimethyl malonate, and indole.

Table 1
Optimization of the reaction of alkylidene malonate **1a** and alkylidene acetoacetate **1b** with indole

| Entry ^a | Reagent | Solvent | Lewis acid | Yield ^b (%) | | |
|--------------------|-----------|------------------------|---------------------------|------------------------|----------|----------|
| | | | | 2 | 3 | 4 |
| 1 | 1a | Toluene | $\text{Yb}(\text{OTf})_3$ | 28 | 36 | — |
| 2 | 1a | DMF | $\text{Yb}(\text{OTf})_3$ | 41 | 21 | 15 |
| 3 | 1a | CH_3CN | $\text{Yb}(\text{OTf})_3$ | 6 | 29 | — |
| 4 | 1a | DMF | $\text{Cu}(\text{OTf})_2$ | 51 | 21 | 7 |
| 5 | 1a | DMF | $\text{Zn}(\text{OTf})_2$ | 18 | — | 5 |
| 6 | 1a | DMF | $\text{Sc}(\text{OTf})_3$ | 57 | — | 16 |
| 7 | 1b | DMF | $\text{Yb}(\text{OTf})_3$ | 19 | 9 | 55 |
| 8 | 1b | DMF | $\text{Cu}(\text{OTf})_2$ | — | 12 | 75 |
| 9 | 1b | DMF | $\text{Zn}(\text{OTf})_2$ | — | 9 | 38 |
| 10 | 1b | DMF | $\text{Sc}(\text{OTf})_3$ | 41 | 7 | 44 |
| 11 | 1b | DMF | — | — | 18 | — |

^a Microwave power 250 W for 20 min.

^b Yields were calculated both by integration of ^1H NMR signals and by integration of HPLC peaks. The remaining amount is unreacted alkylidene malonate.

On the basis of previously reported methods,¹⁰ we choose to begin our screening by using $\text{Yb}(\text{OTf})_3$ as catalyst in different solvents (entries 1–3). When toluene or acetonitrile was used to dissolve the reagents, compound **3** was obtained as the major product. On the contrary, the reaction performed in DMF gave better results: the desired adduct **2a** could be isolated in 41% yield. The formation of bis-indolic derivative **3** can be easily rationalized in the one pot reaction, where a double addition of indole to the aldehyde is assumed, but this is quite unexpected starting from purified alkylidene malonate. As already suggested by Gao and Wu,¹⁵ the adduct **2** is probably converted into a reactive indolenine derivative¹⁶ by the loss of the active methylene fragment, which reacts with another molecule of indole (Fig. 2).

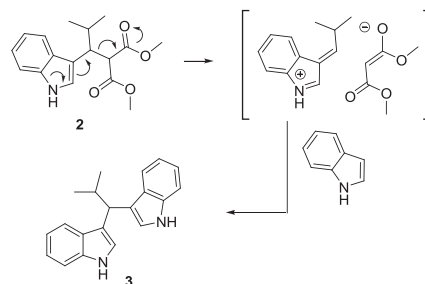


Fig. 2. Proposed mechanism of formation of bis-indole derivative **3** starting from adduct **2**.

We then selected the optimal catalyst, by changing the metal salt. In the presence of $\text{Cu}(\text{OTf})_2$, compound **2a** could be isolated in 51% yield, but evolution into compound **3** (21%) and decarboxylation to **4a** (5%) was always observed (entry 4). On the contrary, $\text{Zn}(\text{OTf})_2$ was not an efficient catalyst affording, under the same conditions, a very low yield of product (entry 5). The reaction performed in the presence of $\text{Sc}(\text{OTf})_3$ afforded a satisfactory amount of product (entry 6), while completely avoiding the formation of undesired bis-indolic derivative **3**. Attempts to enhance the yield by changing microwave power or reaction times did not afford any advantage, since an increase in the side-products was always observed.

Following the same approach, the reaction with acetoacetate **1b** was studied step by step. Optimization of the first step was previously developed, as reported above.¹³ Concerning the conjugate addition, the reaction of indole with alkylidene acetoacetate has been less explored than the corresponding reaction on alkylidene malonate. This is probably due to the fact that, in this case, the newly formed adduct has two stereocenters and, unfortunately, maintenance of diastereocontrol is quite difficult due to the strong

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