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# Ytterbium triflate catalyzed synthesis of β-functionalized indole derivatives

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#### 1. Introduction

Multicomponent reactions (MCRs) represent nowadays a novel and challenging frontier in synthetic organic chemistry. In this kind of processes three or more components react in the same vessel leading to the final product without the need of isolating any intermediates. Since the very beginning of their validation and application, MCRs proved to be a very useful tool for the synthesis of structurally complex molecules, in particular natural products, and in the field of drug discovery. Several examples of 'classic' organic processes were recently described in terms of a MCR version.<sup>1,2</sup> In 1978 Yonemitsu and co-workers discovered a multicomponent-based process by which differently substituted indoles, aldehydes, and Meldrum's acid reacted to give tryptophan derivatives in good vields. Since its first application in organic synthesis,<sup>3</sup> the Yonemitsu reaction has been largely applied to the synthesis of biologically active products, mainly alkaloids, among which are  $\beta$ -substituted tryptophans, tryptamines,  $\beta$ -carbolines, and carbazoles.<sup>4</sup> This type of condensation has been routinely carried out with organic bases employed as promoters, like DL-proline.<sup>5</sup> In some instances the reaction is effective also in absence of catalysts and/or promoters, although there is only one case described in the literature [e.g., the synthesis of gem-(β-dicarbonyl)arylmethanes from indole and hydroxycoumarins].<sup>6</sup> The major limitation of the original Yonemitsu protocol is represented by the fact that the process leads to the desired

## ABSTRACT

Ytterbium triflate was shown to be effective in promoting the synthesis of substituted indole derivatives starting from indole, aldehydes, and dimethyl malonate by a Yonemitsu-type three component reaction. The whole process was carried out in solvent-free conditions and furnished the desired adducts in 42–67% yield.

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adducts only using Meldrum's acid, while it failed or was poorly efficient with other active methylene substrates. Only recently, the search for new and alternative methods using both differently substituted 1,3-dicarbonyl derivatives, other than Meldrum's acid and Lewis acids as catalysts, instead of Brønsted bases, to promote this kind of three component condensation became subject of a growing interest. However, until now only the method recently reported by Sapi and co-workers was found to efficiently promote the synthesis of substituted indoles, furans, pyrroles, and imidazoles. This process used Ti(IV)/Et<sub>3</sub>N complexes as catalysts to perform the Yonemitsu-type trimolecular condensation of aromatic heterocycles, aldehydes, and active methylene substrates.<sup>7,8</sup> Notably other Lewis acids, like Al<sup>3+</sup>, Zr<sup>4+</sup>, and Sn<sup>4+</sup> did not promote such a transformation. Although representing an effective method for the synthesis of  $\beta$ -substituted  $\pi$ -rich aromatic compounds, the Yonemitsu-type process described by Sapi and co-workers is affected by some drawbacks: the need of high quantity of the catalyst complex (up to 1:1 molar ratio with substrates) to efficiently convert the substrates into the desired adducts and no recycling of the catalyst. For these reasons this methodology results in expensive and low application for large scale synthesis. So the search for and development of a facile and good-yielding Yonemitsu-type process is still of great importance. During the last 15 years, rare earth metal triflates have been found to be unique Lewis acids since they are water tolerant reusable catalysts and can effectively promote several carbon-carbon and carbon-heteroatom bond-formation reactions in high yield, including MCRs.<sup>9,10</sup> In the course of our investigations we have recently seen that rare





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earth metal triflates are able to efficiently promote a variety of valuable and high yielding C–C bond-forming reactions.<sup>11</sup>

In continuation of our ongoing studies aimed at developing mild and practical protocols for the synthesis of useful building blocks and/or biologically active compounds by using lanthanides as catalysts, and employing water as solvent or solvent-free conditions, herein we wish to report that a multicomponent Yonemitsu-type reaction can be effectively catalyzed by Yb(OTf)<sub>3</sub> hydrate in satisfactory yields using indole, differently substituted aldehydes and dimethyl malonate as a source of active methylene compound to give  $\beta$ -functionalized indole derivatives (Scheme 1).

Meldrum's acid has a pK<sub>a</sub> value by far lower than that of dimethyl malonate (13.7 versus 4.97). So in theory the latter is less prone to yield the enolate anion necessary to begin the process. Anyway the choice of employing the cheaper dimethyl malonate instead of the more expensive Medlrum's acid is addressed by the fact that is well known that  $\beta$ -diketonates readily react with lanthanides to give stable lanthanide/ $\beta$ -diketonate adducts in which the dicarbonyl moiety is strongly coordinated via enolate anion to the metal center.<sup>12</sup> The efficient Michael addition of  $\beta$ -dicarbonyl compounds to several acceptors is an example of the easy formation of enolate anion of active methylene compounds under the catalysis of lanthanide triflates.<sup>11</sup>

As a preliminary test reaction we studied the conversion of an equimolar mixture of indole, benzaldehyde, and dimethyl malonate in the presence of Yb(OTf)<sub>3</sub> as the catalyst. The reaction was optimized by carrying it out under solvent-free conditions with 10 mol % catalyst and heating by ultrasonication for 12 h; after the addition of 1 N NaOH to precipitate Yb<sup>+3</sup> as the hydroxide, the desired adduct was obtained in 67% yield after extraction with Et<sub>2</sub>O and purification by SiO<sub>2</sub> gel column chromatography. Saponification of the ester functions in the adducts was recorded to a limited extent during the described recovery procedure. Sonication revealed to be a key point for the success of the whole process, as the same protocol carried out by heating at temperatures up to 120 °C led to extensive formation of by-products deriving from indole polymerization, oxidation of aldehydes, and aldol condensation. All these were found also in the above reported procedure but in low yields. To investigate the advantages and limitations of our methodology, other aldehydes, having electron withdrawing and donating substituents in the aromatic ring (entries 2-6), as well as aliphatic aldehydes like isopropylcarboxyaldehyde (entry 7) or *n*-hexanal (entry 8) were subsequently used and the results of their condensation with indole and dimethyl malonate are reported in the Table 1.

Both aromatic aldehydes having electron donating or withdrawing substituents as well as aliphatic aldehydes reacted nearly to the same extent furnishing the desired adducts in yields ranging from 42% to 54%. The catalyst was always recovered by precipitation as Yb(OH)<sub>3</sub>, filtrated, and transformed into



Scheme 1



$\beta(O11)_3$ catalyzed synthesis of $\beta$ -functionalized indole derivative
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 $^{\rm a}$  Yields of pure isolated products, characterized by IR, GC–MS,  $^{\rm 1}{\rm H}$  NMR, and  $^{\rm 13}{\rm C}$  NMR.

the triflate salt as already described.<sup>13</sup> Recycled in this way, the catalyst could be reused several times without any significant loss of activity. For example the reaction leading to product of entry 1 was repeated three additional times with the recovered Lewis acid with yields in indole derivatives of 63%, 65%, and 62%, respectively.

The same reaction was also performed by using other metal triflates from the lanthanide series, but the results were worse than with Yb(OTf)<sub>3</sub>. The reason of this discrepancy of catalytic efficiency in the lanthanide series could be explained by the fact that Yb<sup>+3</sup> is the "hardest" cation and thus the most oxophilic, due to its smaller ionic radius.<sup>14</sup> So, coordination of the oxygen atoms of dimethyl malonate and aldehyde to Yb<sup>+3</sup> would result in a greater enhancement of the reactivity of substrates participating to the multicomponent Yonemitsu-type condensation we are dealing with. It's also interesting to note that the use of Meldrum's acid instead of dimethyl malonate under the same experimental conditions resulted in no reactions. This difference in reactivity may be explained by the fact that malonates can adopt a *cis* configuration of the corresponding enolate leading to a more efficient chelation on the metal center.<sup>12</sup>

From a mechanistic point of view, it could be hypothesized that  $Yb^{+3}$  first coordinates dimethyl malonate yielding a highly reactive enolate species, that in turn could give an aldol condensation with the aldehyde yielding an  $\alpha,\beta$ -unsaturated intermediate, still coordinated to the lanthanide in the  $\beta$ -dicarbonyl portion. In fact the reaction of only dimethyl malonate and aldehydes in the presence of  $Yb(OTf)_3$  promptly led to this kind of adduct. The formation of the  $\alpha,\beta$ -unsaturated intermediate would result in a great enhancement of the electrophilicity of adduct to which indole could easily add leading to the desired product.

As a conclusion, in this manuscript we have demonstrated that indole and differently substituted aldehydes undergo an efficient condensation reaction with dimethyl malonate under the catalysis of  $Yb(OTf)_3$  hydrate. The simple workup procedure, mild reaction conditions, and satisfactory yields make our methodology a valid and alternative contribution to the existing processes in the field of the multicomponent Yonemitsu-type condensations. To the best of our knowledge, the process described herein represents the first example of the Yonemitsu reaction catalyzed by a Lewis acid without the addition of other promoters like amines. Moreover, this protocol introduces a practical and viable technology of solvent-free reactions. Further investigations to broaden the scope of this methodology are in progress in our laboratories.

## 2. Experimental

## 2.1. General remarks

All reagents were obtained from commercial sources (Aldrich Chemical Co.) and used without further purification. All solvents were of analytical grade. All extracts were dried over anyhdrous Na<sub>2</sub>SO<sub>4</sub>. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AC 200 (<sup>1</sup>H NMR, 200 MHz; <sup>13</sup>C NMR, 50.32 MHz) CDCl<sub>3</sub> was used as the solvent and tetramethylsilane as an internal standard. Chemical shifts are reported in  $\delta$  (ppm). Reactions were routinely monitored by TLC using Merck silica gel F<sub>254</sub> plates and visualization of TLC spots with a freshly prepared 7% ethanolic solution of phosphomolybdic acid. Silica gel 40 (0.063–0.200 mm) from Merck was used for column chromatography. Melting points were measured on a Büchi melting point apparatus and are uncorrected. Elemental analyses were carried out on a Carlo Erba 1106 elemental analyzer. The purity of the intermediates and the final products was confirmed by combustion analysis.

#### 2.2. General procedure

To a mixture of indole (1.0 mmol), dimethyl malonate (1.0 mmol), and aldehyde (1.0 mmol), Yb(OTf)<sub>3</sub> hydrate (0.1 mmol) was added and the resulting suspension was sonicated in an ultrasound bath for 12 h. After the completion of the reaction, monitored by TLC (elution mixture  $CH_2Cl_2$ /petroleum ether 9:1), NaOH 1 N (20 mL) was poured into the mixture, that was then filtered and the filtrate washed and extracted with Et<sub>2</sub>O (3 × 10 mL). The collected organic phases were evaporated to dryness and the resulting crude mixture was purified by SiO<sub>2</sub> gel column chromatography (eluent  $CH_2Cl_2$ ), yielding the desired adduct. The catalyst was recovered and recycled as already described.<sup>10</sup>

*Dimethyl* 2-[1H-indol-3-yl(phenyl)methyl]malonate (entry 1): Yield = 67% as a white solid, mp = 150–151 °C (*n*-hexane). Analytical data were identical to those already reported for the same compound.<sup>6</sup> Anal. Calcd for  $C_{20}H_{19}NO_4$ : C, 71.20; H, 5.68; N, 4.15; O, 18.97. Found: C, 71.16; H, 5.67; N, 4.12; O, 18.98.

Dimethyl 2-[1H-indol-3-yl(4-nitrophenyl)methyl]malonate (entry 2): Yield = 54% as a pale red solid, mp = 146–148 °C (*n*-hexane). Analytical data were identical to those already reported for the same compound.<sup>6</sup> Anal. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>: C, 62.82; H, 4.74; N, 7.33; O, 25.11. Found: C, 62.85; H, 4.73; N, 7.32; O, 25.12.

Dimethyl 2-[(4-hydroxyphenyl)(1H-indol-3-yl)methyl]malonate (entry 3): Yield = 47% as a pale yellow solid, mp =  $172-174 \degree C$  (*n*-hexane). <sup>1</sup>H NMR  $\delta$  3.61 (s, 3H), 3.63 (s, 3H), 4.28 (d, 1H, J = 11.6 Hz), 5.08 (d, 1H, J = 11.6 Hz), 6.64–7.52 (m, 9H), 7.94 (s br, 1H), 8.17 (s br, 1H); <sup>13</sup>C NMR  $\delta$  38.4, 52.4, 57.7, 110.5, 111.8, 117.7, 117.8, 119.1, 120.9, 121.6, 125.7, 128.6, 128.7, 129.1, 138.0, 138.9, 153.5, 168.8, 169.2; IR (neat, cm<sup>-1</sup>) 3600 (br), 1710. Anal. Calcd for C<sub>20</sub>H<sub>19</sub>NO<sub>5</sub>: C, 67.98; H, 5.42; N, 3.96; O, 22.64. Found: C, 67.99; H, 5.44; N, 3.94; O, 22.62.

Dimethyl 2-[(4-fluorophenyl)(1H-indol-3-yl)methyl]malonate (entry 4): Yield = 42% as a pale yellow solid, mp = 158–159 °C (*n*-hexane). <sup>1</sup>H NMR δ 3.62 (s, 3H), 3.66 (s, 3H), 4.22 (d, 1H, *J* = 11.8 Hz), 5.12 (d, 1H, *J* = 11.8 Hz), 7.08–7.67 (m, 9H), 8.20 (s br, 1H); <sup>13</sup>C NMR δ 38.3, 52.3, 57.9, 110.3, 111.1, 117.6, 118.3, 120.2, 121.5, 125.5, 128.6, 128.7, 129.4, 138.2, 142.0, 142.1, 155.5, 162.0, 168.6, 169.5. IR (neat, cm<sup>-1</sup>) 1711. Anal. Calcd for C<sub>20</sub>H<sub>18</sub>FNO<sub>4</sub>: C, 67.60; H, 5.11; N, 3.94; O, 18.01. Found: C, 67.62; H, 5.12; N, 3.95; O, 18.02.

*Dimethyl* 2-[(4-chlorophenyl)(1H-indol-3-yl)methyl]malonate (entry 5): Yield = 47% as a white solid, mp = 162−164 °C (*n*-hexane). <sup>1</sup>H NMR δ 3.65 (s, 3H), 3.68 (s, 3H), 4.28 (d, 1H, *J* = 11.7 Hz), 5.18 (d, 1H, *J* = 11.7 Hz), 7.02−7.62 (m, 9H), 8.15 (s br, 1H); <sup>13</sup>C NMR δ 38.2, 52.1, 57.6, 110.3, 111.4, 119.1, 120.2, 121.7, 122.7, 122.8, 125.6, 129.0, 129.6, 130.2, 130.3, 137.8, 144.9, 168.9, 169.4. IR (neat, cm <sup>-1</sup>) 1713. Anal. Calcd for C<sub>20</sub>H<sub>18</sub>CINO<sub>4</sub>: C, 64.61; H, 4.88; N, 3.77; O, 17.21. Found: C, 64.63; H, 4.87; N, 3.75; O, 17.22.

*Dimethyl* 2-[1H-indol-3-yl(3-nitrophenyl)methyl]malonate (entry 6): Yield = 47% as a pale brown solid, mp = 147–149 °C (*n*-hexane). <sup>1</sup>H NMR δ 3.65 (s, 3H), 3.69 (s, 3H), 4.26 (d, 1H, J = 11.9 Hz), 5.12 (d, 1H, J = 11.9 Hz), 7.16–8.23 (m, 9H), 8.28 (s br, 1H); <sup>13</sup>C NMR δ 38.8, 52.4, 57.8, 110.1, 111.5, 119.9, 120.2, 120.8, 121.5, 123.7, 125.7, 127.0, 128.6, 132.7, 138.1, 144.9, 150.6, 169.1, 169.2. IR (neat, cm<sup>-1</sup>) 1715, 1556, 1361. Anal. Calcd for C<sub>20</sub>H<sub>18</sub>N<sub>2</sub>O<sub>6</sub>: C, 62.82; H, 4.74; N, 7.33; O, 25.11. Found: C, 62.83; H, 4.75; N, 7.34; O, 25.12.

*Dimethyl* 2-[1-(1H-indol-3-yl)-2-methylpropyl]malonate (entry 7): Yield = 44% as a white solid, mp = 127–128 °C (*n*-hexane). Analytical data were identical to those already reported for the same compound.<sup>6</sup> Anal. Calcd for  $C_{17}H_{21}NO_4$ : C, 67.31; H, 6.98; N, 4.62; O, 21.10. Found: C, 67.33; H, 6.94; N, 4.61; O, 21.12.

Dimethyl 2-[1-(1H-indol-3-yl)hexyl]malonate (entry 8): Yield = 43% as a pale yellow solid, mp = 138–140 °C (*n*-hexane). <sup>1</sup>H NMR δ 0.89 (t, 3H, J = 7.7 Hz), 1.12–1.43 (m, 8H), 3.42 (s, 3H), 3.43 (s, 3H), 3.86 (dt, 1H, J = 10.2 Hz, J = 3.2 Hz), 4.94 (d, 1H, J = 10.2 Hz), 7.02–7.88 (m, 5H), 8.15 (s br, 1H); <sup>13</sup>C NMR  $\delta$  14.1, 22.7, 33.1, 33.4, 35.6, 38.7, 52.4, 57.8, 110.9, 111.0, 118.7, 119.3, 121.9, 124.0, 129.2, 137.0, 169.0, 170.1. IR (neat, cm<sup>-1</sup>) 1712. Anal. Calcd for C<sub>19</sub>H<sub>25</sub>NO<sub>4</sub>: C, 68.86; H, 7.60; N, 4.23; O, 19.31. Found: C, 68.88; H, 7.58; N, 4.21; O, 19.30

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