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Studies and Mechanism of Olefination Reaction in Aryl-Enolates with Paraformaldehyde

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Abstract

A simple, efficient and low-cost methodology for the synthesis of *α*-aryl-*α*,*β*-unsaturated esters using paraformaldehyde as a source of carbon was developed. Factors that control reaction yields such as temperature, concentration and reaction time were evaluated. A mechanism is proposed based on experimental structures of the intermediates.

Keywords

Olefination, Paraformaldehyde, *α*-Aryl-*α*,*β*-Unsaturated Ester, *α*-Methylenation

1. Introduction

The *α*-substituted acrylic acid analogs or derivatives are a dynamic key synthon in the construction of interesting molecules due to their capacity to act as Michael acceptors [1] [2] [3] [4] [5], Diels-Alder dienes [6] or Aza-Morita-Baylis-Hillman reaction substrates [7]. These molecules include drugs, bioactive compounds, process impurities and advanced synthetic intermediates [8] [9]. As a result, several methods to synthesize these synthons have been reported (**Figure 1**) [10] [11].

One of the most common choices of aldehyde for *α*-substituted-*α*,*β*-unsaturated compound through aldol condensation is formaldehyde where the reaction is typically known as *α*-methylenation [12] [13] [14].

Excellent works about the use of aqueous formaldehyde as methylenation agent *via* Mannich reaction have been published. For example, in 2006, Erkkilä and Pihko have performed the formation of *α*-methylenated aldehydes, also

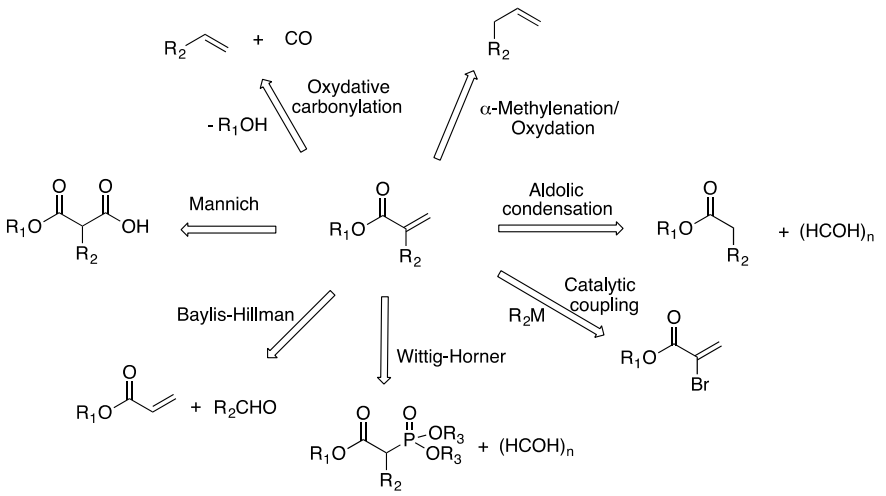


Figure 1. Strategies for the synthesis of acrylates.

called *α*-substituted acroleines, using aqueous formaldehyde and secondary amines as a catalyst [12]. Several studies employing other aldehydes and different types of alkyl, cyclic, aryl ketones and esters have been developed using diisopropylammonium trifluoroacetate salt [13] or Meldrum's acid as a catalyst.

On the other hand, and in addition to Mannich reaction, one of the most useful strategies for the formation of *α*,*β*-unsaturated systems is the aldol condensation [15] [16] due to its efficiency and low cost. In this transformation, the *α*-carbon of an enolate is bonded with the carbonyl carbon of an aldehyde, and a *β*-hydroxylated-carbonyl intermediate is obtained. Most of the times, a *β*-dehydration is observed as part of the process, and an *α*,*β*-unsaturated compound is isolated. On the other hand, when a functionalized aldehyde is employed, a *trans*-*β*-substituted-*α*,*β*-unsaturated compound is obtained [17] [18]. Rodriguez *et al.* [19] reported that when both enolate and aldehyde are functionalized, the corresponding product is an *α*,*β*-disubstituted-*α*,*β*-unsaturated compound. They also mentioned that with this method, stereochemistry control of this reaction proved to be nontrivial.

Even though the aldol reaction employing formaldehyde is useful in the formation of *α*-methylenated carbonyl compounds, there are few reports about its use. One of the early reports was that of Laos in 1967 [20] where the *α*-methylenation of steroidal ketones was carried out with aqueous formaldehyde and potassium acetate as base and methanol or water as solvents. Recently, Liu studied the effect of the acidity of zeolite in the formation of acrylic acid and methyl acrylate from formaldehyde and methyl acetate [21].

A useful and practical source of formaldehyde is paraformaldehyde, a polymer, due to it is a versatile and easily handled reactively. For example, Amri *et al.* [22] used paraformaldehyde as homologate agent by substituting phosphonate group in the Honer-Wadsworth-Emmons reaction type synthesis of (±)-homosarkomycin with 98% of yield. An aldol type *α*-methylenation of lactones employing paraformaldehyde, which gives moderate to good yields was performed

by Tanaka and Yamashita [23]. Chen *et al.* [24] also prepared *α*-nitro ethyl acrylate intermediates using paraformaldehyde, which was then employed as Michael acceptor in the synthesis of tryptophan derivatives.

Traditionally, it is accepted that aqueous formaldehyde and paraformaldehyde are two different sources of the same monomeric reactive and that the only advantage that paraformaldehyde has is that it can be used in water free reactions or solvents.

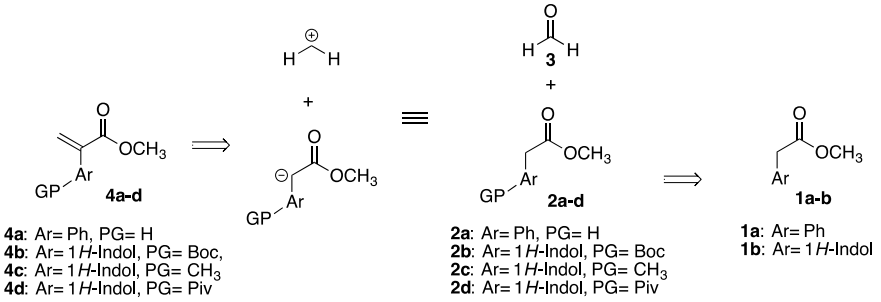
In the present work, we propose a possible mechanistic pathway of aldol condensation using paraformaldehyde, which is different from that observed in formaldehyde.

2. Results and Discussion

2.1. Reaction of Methyl Phenylacetate (1a) with Sodium Hydride and Paraformaldehyde (3)

Currently, our research group is interested in the synthesis of β^2-and β^3-amino acids *via* aza-Michael addition to *α,β*-unsaturated esters [25]. One of our method of choice is a facile synthesis of 2-aryl methyl acrylates (4a-d); retrosynthetic approximation is shown in Scheme 1.

In the present study, initially, methyl phenylacetate (**1a**), paraformaldehyde (**3**) and NaH were chosen as starting materials. Acrylate **4a** synthesis was carried out using toluene as solvent and microwave (MW) heating. Table 1 and Scheme 2 summarize experimental results for different solvents, reaction times, and sources of activation energy.

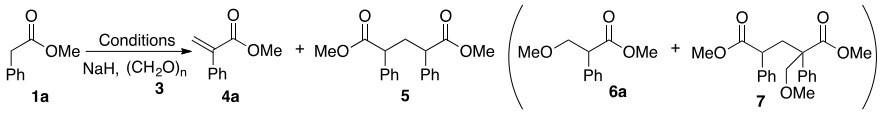


Scheme 1. Retrosynthetic analysis for the preparation of 2-aryl methyl acrylates.

Table 1. Reaction conditions and yields for the aldol condensation of **1a** and **3**.

Entry	1a (mmol)	3 (eq)	NaH (eq)	Solvent	Source energy activation	Time (h)	Yield (%)			
							4a	**5**	**6a**	**7**
1	3.3	3	1.5	Toluene	MW	1	-[a]	55	-	-
2	3.3	9	3	Toluene	MW	3	60	-	-	-
3	16.6	9	3	Toluene	MW	1.5	87	-	-	-
4	66.6	9	3	Toluene	r. t.	1.6	11	-	29	5
5	33.3	9	3	Toluene	55˚C[b]	1	87	-	-	-
6	33.3	9	3	THF	55˚C[b]	0.25	62	-	-	-

a. Traces of product **4a**, b. Temperature of addition of the reagents.



Scheme 2. Aldol condensation reaction of 1a and 3.

The first entry in Table 1 shows the result of the formation of the acrylate **4a** using 1.5 equiv. of NaH in toluene and MW heating for 1 h. Compound **5** was isolated as the main product with 55% yield and only traces of **4a** (entry 1). An increase of paraformaldehyde from 3 to 9 equiv. and of NaH from 1.5 to 3 equiv., results in a better yield (60%) of acrylate **4a** (entry 2). On the other hand, when the reaction is carried out with 16.6 mmol of **1a**, acrylate **4a** was isolated in higher yield (87% yield, entry 3). When the reaction is carried out at room temperature, **4a** was obtained with a smaller yield and **6a**, and **7** were also produced in 29% and 5% yields, respectively (entry 4). For this last experiment, it is relevant mentioning that after 1 h, the reaction spontaneously generated an exothermic from 25˚C to 55˚C.

When the reaction was carried out at 55˚C, after 1 h only **4a** was obtained with 87% yield (entry 5). The result suggests that temperature can be used to control the production of byproducts **6a** and **7a**. Finally, in order to explore the solvent effect, the reaction was carried out in THF at the same temperature with a better yield of **4a** in only 15 min (entry 6).

Scheme 3 proposes a reaction mechanism for the formation of **4a**, **5**, **6a**, and **7**. The enolate of **1a** carried out a nucleophilic substitution over paraformaldehyde, and the intermediate **10** was produced.

From there on, the reaction could generate **4a** through a β-elimination (E_β, Path 1) and subsequently a Michael addition of the enolate of **1a** on **4a** to form the corresponding compound **5**.

Alternatively, two products could be generated *via* Path 2. **6a** is obtained through a nucleophilic substitution by the hydride; and **7** was isolated through the Michael addition of **4a** and the enolate **6a**.

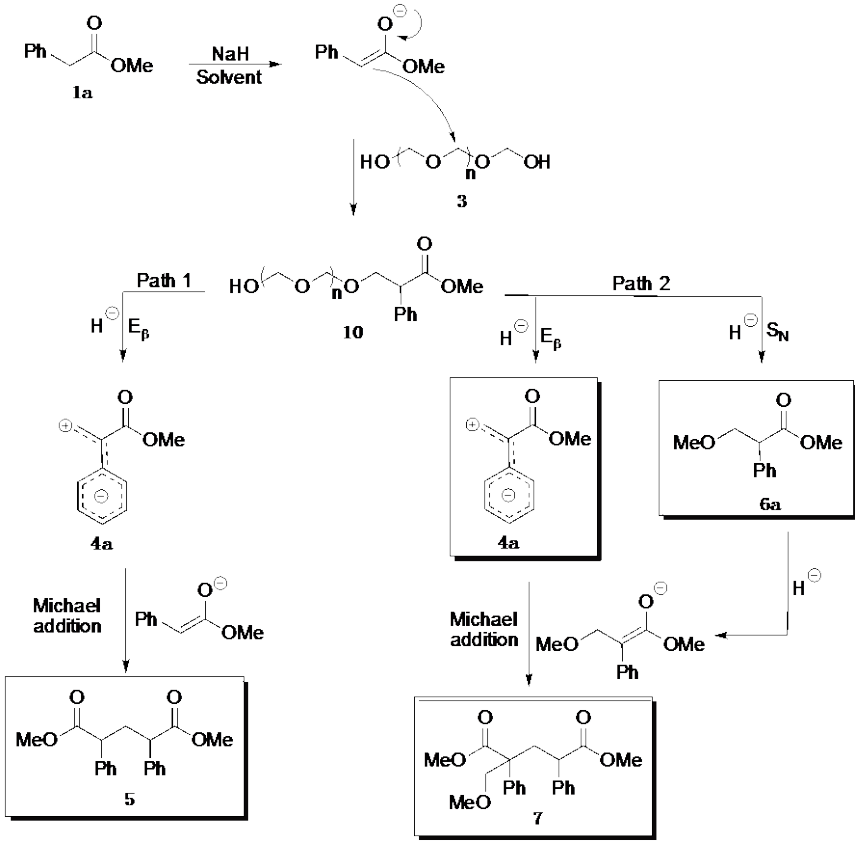
Recrystallization of **7**, afforded a suitable crystal for X-ray diffraction analysis. The resulting structure is presented in Figure 2.

2.2. Synthesis of Acrylates Derivatives 4b, 4c, and 4d

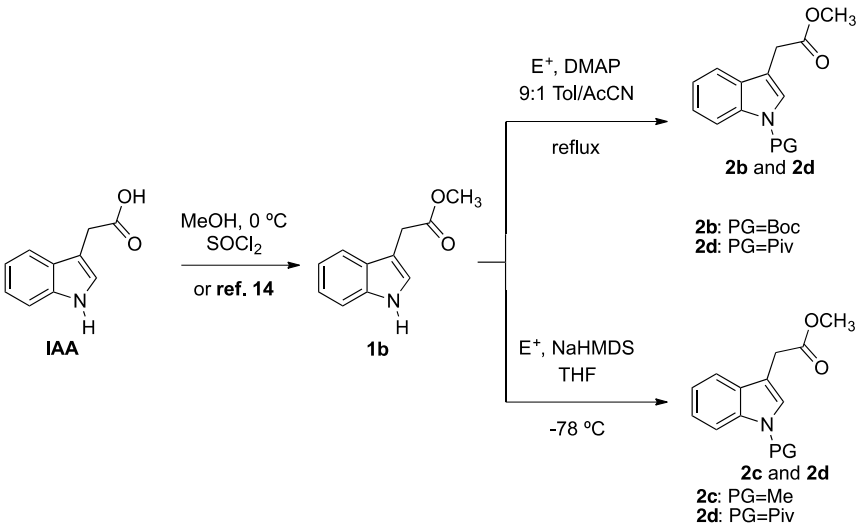
We chose to examine the synthesis of other acrylates: **4b**, **4c**, and **4d** under the conditions of entry 6 in Table 1 which are optimized from the reaction time and solvent choice point of view. For this purpose, we first synthesized **2b**, **2c,** and **2d** (see Scheme 4).

Due to the structural diversity presented in methyl esters **2b**, **2c**, and **2d**, a general synthetic route to these compounds was not available. Below, we describe two methodologies, including some developed by our research group.

Compound **1b** was first esterified with methanol in the presence of TMSCl. **2b** and **2d** were then synthesized through of the addition of $(Boc)_2O$ or pivaloyl



Scheme 3. Mechanism approach for the isolation of byproducts 5, 6a and 7.



Scheme 4. Syntheses of derivatives 2b-d.

chloride, with 4-DMPA as a catalyst in a mixture of Toluene/AcCN 9:1 as solvent at reflux. On the other hand, **2d** can also be produced by the addition of NaHMDS to **1b** in THF at −78˚C.

Recrystallization of **2d** afforded suitable crystal for X-ray diffraction analysis shown in Figure 3.

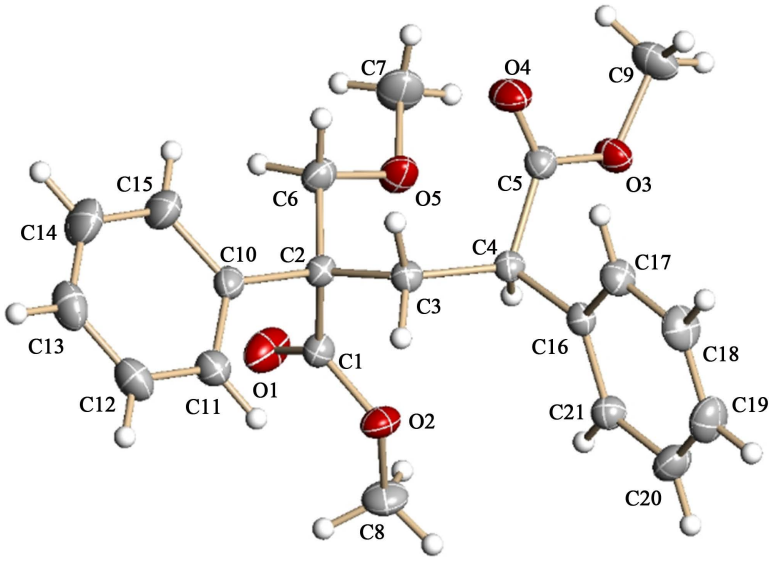


Figure 2. X-ray structure of **7**.

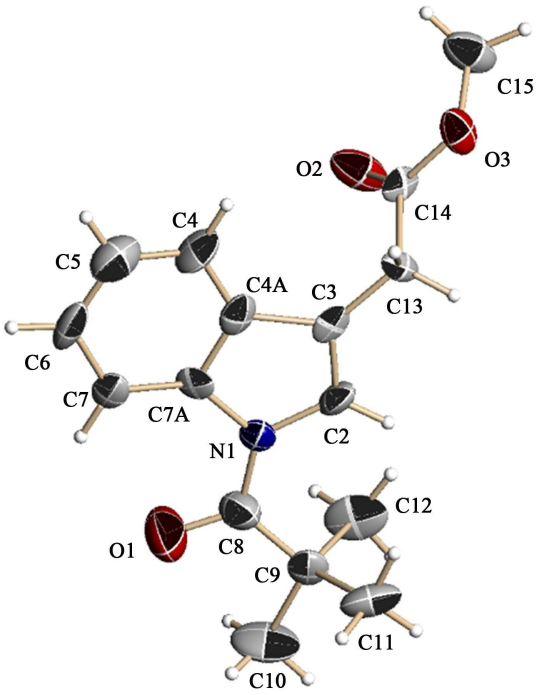
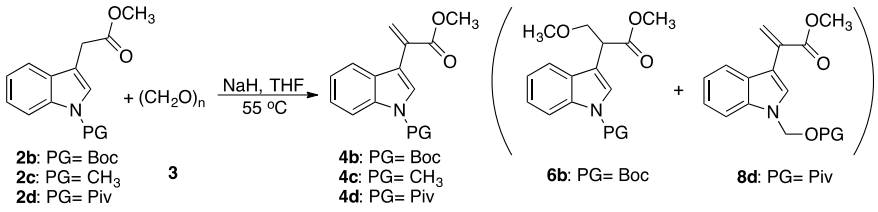


Figure 3. X-ray structure of **2d**.

Having produced **2b**, **2c,** and **2d**, we then proceed with the syntheses of the acrylates **4b**, **4c**, and **4d**. The results of this series are summarized in Table 2.

As expected from the results shown in Table 1, the desired acrylates derivatives **4b** and **4c** were obtained in 50% and 62% yield respectively. After purification of **4b** by column chromatography, traces of **6b** were found (entries 1 and 2, Table 2 and Scheme 5). It is worth mentioning that the product **4d** could not be obtained under these reaction conditions, but surprisingly one side product (**8d**) was isolated in 37% yield.



Scheme 5. Aldol condensation reaction of 2a-c and 3.

Table 2. Reaction conditions and yields for the aldol condensation of **2b-d** with **3**.

Entry	2	PG	3 (eq)	NaH (eq)	Time (h)	4 (%)	6 (%)	8 (%)
1	**b**	Boc	9	3	0.25	50	-[a]	-
2	**c**	Me	9	3	0.25	62	-	-
3	**d**	Piv	9	3	0.25	-	-	37

[a]Traces of product **6b**.

Similar to the case of **2b**, here we expect to obtain either **4d** or **6d**. Instead, we found **8d** a product of rearrangement reaction. We hypothesize that this compound formed by the insertion of a -CH_2O-moiety from paraformaldehyde between the protector group and the indole (Scheme 6).

3. Conclusion

In summary, although the classical mechanism for this olefination reaction suggests that the paraformaldehyde is dissociated to formaldehyde when it is warmed, and then it reacts with the enolate to get the aldol product and its subsequent dehydration. However, in this study, we demonstrate that the addition of a carbon atom from paraformaldehyde to give rise to the vinyl group occurs through a series of nucleophilic substitutions catalyzed by hydride over acetalic carbons from the polymer.

4. Experimental

Experimental Materials and Methods

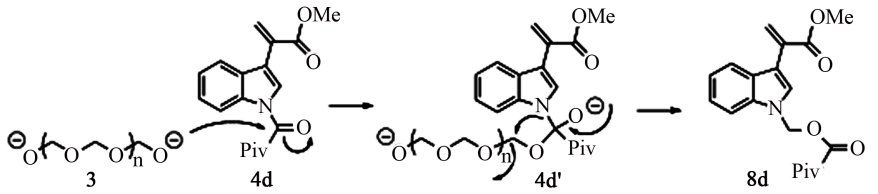
The course of the reactions was followed by TLC. Silica gel of 70 - 230 mesh of Merk (Darmstad, Germany) was used for purification of the products by flash chromatography. Methyl phenyl-acetate (**1a**), 3-indoleacetic acid and paraformaldehyde (**3**) were purchased from Aldrich and used without further purification.

Analytical Methods

Spectra data of ^{1}H NMR and ^{13}C NMR were obtained in $CDCl_3$ solutions with TMS as internal standard on Varian Gemini 200, Varian Oxford 400, and Inova 400 spectrometers. Mass spectral analyses were carried out in a spectrometer JEOL model JMS-AX50SHA.

Methyl 2-(1*H-Indol*-3-*yl*)*Acetate* **1*b***.

In a flask of 250 mL provided with magnetic stirrer, 5.0 g (28.54 mmol) of 3-indolacetic acid and 50 mL of MeOH were added. The flask was cooled at 0˚C



Scheme 6. A proposed mechanism for the formation of **8d**.

and then 2.5 mL (4.08 g, 34.27 mmol, 1.2 equiv.) of thionyl chloride. The mixture was stirred during 1 h, and then a saturated K_2CO_3 solution was added until getting 8 - 9 pH. Methanol was evaporated, and the solution was extracted with ethyl acetate (3 × 30 mL). The organic phase was dried over Na_2SO_4 anhydrous. Concentration in a rotatory evaporator gave the crude product, which was purified by flash chromatography (n-hexane/ethyl acetate, 70:30 - 50:50). Red oil, yield 97%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.72 (s, 3H, O**CH$_3$**); 3.80 (d, ^3J = 0.8 Hz, 2H, **CH$_2$**CO); 7.04 (d, ^3J = 2.4 Hz, H, NH**CH**); 7.18 (m, 2H, **C^{5}H-C^{6}H**); 7.29 (d, ^3J = 8.4 Hz, H, **C^{4}H**); 7.63 (d, ^3J = 7.6 Hz, H, **C^{7}H**); 8.16 (br, s, H, **NH**). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 31.1 (O**CH$_3$**); 31.9 (**CH$_2$**CO); 108.2 (**C-3**); 111.2 (**C-4**); 118.7 (**C-7**); 119.6 (**C-5**); 122.1 (**C-6**); 123.2 (**C-2**); 127.2 (**C$_{ipso}$-3a**); 136.2 (**C$_{ipso}$-7a**); 172.7 (CH$_2$**CO**). HRMS (FAB+): calcd. for $C_{11}H_{11}NO_2$[M$^+$]: 189.2140, found: $C_{11}H_{12}NO_2$[M + H$^+$]: 190.0880.

General procedure 1:

In a flask provided with magnetic stirrer **1b** (or **c**), 1.1 equiv. of $(Boc)_2O$, 0.1 equiv. of 4-DMAP and a 9:1 Toluene: CH_3CN mixture were added. The reaction mixture was refluxed for 3 h. The mixture of solvents was evaporated, and then H_2O was added and extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 anhydrous. Concentration in a rotatory evaporator gave the crude product, which was purified by flash chromatography (n-hexane/ethyl acetate).

General procedure 2:

In a flask provided with a magnetic stirrer and N_2 atmosphere, **1c** (or **d**) and 50 mL of THF anhydrous were added. The flask was cooled at −78˚C and then 1.1 equiv. of NaHMDS and 1.2 equiv. of protective reagent. The mixture was stirred during 2 h, and then a saturated K_2CO_3 solution was added until getting 8 - 9 pH. The solution was extracted with ethyl acetate. The organic phase was dried over Na_2SO_4 anhydrous. Concentration in a rotatory evaporator gave the crude product, which was purified by flash chromatography (n-hexane/ethyl acetate).

General procedure 3:

In a flask of 100 mL provided with magnetic stirrer 5 equiv. of NaH 60% were added to 50 mL of n-hexane. The mixture was stirred during 15 min, the n-hexane was subtracted, and 50 mL of THF were then added. The flask was cooled at 0˚C and then **2**, 9 equiv. of paraformaldehyde were added. The reaction mixture was stirred for 1 h, 20 mL of water were added, and the solution was extracted with diethyl ether (3 × 10 mL). Concentration in a rotatory evaporator gave the crude product, which was purified by flash chromatography

(n-hexane/ethyl acetate).

tert-Butyl 3-(2-*Methoxy*-2-*Oxoethyl*)-1*H-Indole*-1-*Carboxylate* **2*b***.

According to General Procedure 2, in a flask of 250 mL, 5.0 g (26.43 mmol) of **1b**, 6.34 g (29.068 mmol) of $(Boc)_2O$, 0.32 g (2.64 mmol) of 4-DMAP and 100 mL of a 9:1 Toluene:AcCN mixture were added. Green solid, yield 97%. m.p.: 58 °C. ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 1.96 (s, 9H, OC**(CH$_3$)$_3$**); 4.01 (s, 5H, **CH$_2$**COO**CH$_3$**); 7.58 (m, 2H, **C^{5}H-C^{6}H**); 7.82 (d, ^3J = 8.0 Hz, H, **C^{4}H**); 7.87 (s, H, N**CH**); 8.45 (d, ^3J = 8.0 Hz, H, **C^{7}H**). ^{13}C NMR ($CDCl_3$, 50 MHz), δ (ppm): 28.4 (OC**(CH$_3$)$_3$**); 31.1 (O**CH$_3$**); 52.3 (**CH$_2$**CO); 83.8 (O**C**$(CH_3)_3$); 113.2 (**C-3**); 115.4 (**C-7**); 119.1 (**C-4**); 122.7 (**C-6**); 124.5 (**C-5**); 124.6 (**C-2**); 130.1 (**C$_{ipso}$-3a**); 135.5 (**C$_{ipso}$-7a**); 149.6 (O**CO**N); 171.5 (CH_2**CO**). Anal. Calcd. for $C_{16}H_{19}NO_4$: C 66.42, H 6.62; N, 4.84; found: C 66.10, H 6.49, N 4.66.

Methyl 2-(1-*Methyl*-1*H-Indol*-3-*yl*)*Acetate* **2*c***.

According to General Procedure 2, 0.48 g (2.54 mmol) of **1b**, 2.8 mL (2.8 mmol) of NaHMDS and 0.19 mL (3.04 mmol) of iodomethane were added. Colorless oil, yield 29%. ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 3.68 (s, 3H, N**CH$_3$**); 3.73 (s, 3H, O**CH$_3$**); 3.76 (s, 2H, **CH$_2$**CO); 7.02 (s, H, N**CH**); 7.14 (m, *2*H, **C^{5}H-C^{6}H**); 7.28 (d, ^3J = 7.0 Hz, H, **C^{4}H**); 7.58 (d, ^3J = 10.0 Hz, H, **C^{7}H**). ^{13}C NMR ($CDCl_3$, 50 MHz), δ (ppm): 31.2 (N**CH$_3$**); 32.8 (O**CH$_3$**); 52.0 (**CH$_2$**CO); 105.1 (**C-3**); 106.9 (**C-4**); 109.4 (**C-7**); 119.0 (**C-5**); 119.3 (**C-6**); 121.9 (**C-2**); 127.8 (**C$_{ipso}$-7a**); 137.0 (**C$_{ipso}$-3a**); 172.7 (CH_2**CO**). HRMS (FAB+): calcd. for $C_{12}H_{13}NO_2$[M$^+$]: 203.2410, found: $C_{12}H_{13}NO_2$ [M$^+$]: 203.0946.

Methyl 2-(1-*Pivaloyl*-1*H-Indol*-3-*yl*)*Acetate* **2*d***.

According to General Procedure 2, 0.5 g (2.64 mmol) of methyl **1b**, 2.9 mL (2.9 mmol) of NaHMDS and 0.39 mL (3.17 mmol) of trimethylacetyl chloride were added. Colorless solid, yield 29%. m.p.: 108˚C - 111˚C. ^{1}H NMR ($CDCl_3$, 200 MHz), δ (ppm): 1.52 (s, 9H, **(CH$_3$)$_3$**CO); 3.74 (s, 3H, O**CH$_3$**); 3.75 (d, ^3J = 2.0 Hz, 2H, **CH$_2$**CO); 7.32 (m, 2H, **C^{5}H-C^{6}H**); 7.52 (d, ^3J = 8.0 Hz, H, **C^{4}H**); 7.80 (s, H, N**CH**); 8.51 (d, ^3J = 8.0 Hz, H, **C^{7}H**). ^{13}C NMR ($CDCl_3$, 50 MHz), δ (ppm): 28.6 (OC**(CH$_3$)$_3$**); 30.7 (O**CH$_3$**); 41.2 (O**C**$(CH_3)_3$); 52.1 (**CH$_2$**CO); 104.9 (**C-3**); 113.8 (**C-7**); 117.4 (**C-4**); 118.4 (**C-6**); 123.5 (**C-5**); 124.2 (**C-2**); 129.0 (**C$_{ipso}$-3a**); 136.9 (**C$_{ipso}$-7a**); 171.3 ($(CH_3)_3$**CO**); 176.8 (CH_2**CO**). HRMS (FAB+): calcd. for $C_{16}H_{19}NO_3$ [M$^+$]: 273.3320, found: $C_{16}H_{20}NO_3$ [M + H$^+$]: 274.1457. X-Ray crystallographic structure in **Figure 2** [26].

Methyl 2-*Phenyl-Acrylate* **4*a***.

In a flask of 250 mL provided with a magnetic stirrer and N_2 atmosphere 4.0 g (100 mmol, 3 equiv.) of NaH 60% were added to 50 mL of n-hexane. The mixture was stirred during 15 min, the n-hexane was subtracted, and 125 mL of THF was then added. The flask was cooled at 0˚C, and then 5 g (33.31 mmol, 1 equiv.) of **2a**, 9 g (299.9 mmol, 9 equiv.) of paraformaldehyde was added. The reaction mixture was heated to 50˚C - 53˚C for around 8 min, intense reflux was initiated, and the mixture immediately turns yellow. Then 50 mL of water was added, and the solution was extracted with ethyl acetate (3 × 20 mL). Concentration in a rotatory evaporator gave the crude product, which was purified by flash

chromatography (n-hexane/ethyl acetate, 80:20 - 60:40). Colorless oil, yield 87%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.81 (s, 3H, **CH_3**O); 5.88 (d, J = 1.2 Hz, 1H, **$CH_{b\text{-}gem}$**), 6.36 (d, J = 1.2, 1H, **$CH_{a\text{-}gem}$**), 7.10 - 7.41 (m, 5H, **Ph**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.3 (**CH_3**O), 126.9 (**CH_2**=C), 128.2 (**C**Ph), 128.3 (**C**Ph), 128.4 (**C**Ph), 136.8 (C_{ipso}-Ph), 141.4 (**C**=CH_2), 167.3 (**C**OOCH_3). HRMS (EI): calcd. for $C_{10}H_{10}O_2[M]^+$: 162.0681, found: $C_{10}H_{10}O_2$: 162.0070.

tert-Butyl 3-(3-*Methoxy*-3-*Oxoprop*-1-*en*-2-*yl*)-1*H-Indole*-1-*Carboxylate* ***4b***.

According to General Procedure 3, 0.52 g (1.8 mmol) of **2b,** 0.36 g (9 mmol) of NaH 60% and 0.486 g (16.18 mmol) of paraformaldehyde were added. Green oil, yield 50%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.28 (s, 9H, OC**$(CH_3)_3$**); 3.35 (s, 3H, O**CH_3**); 5.85 (d, $^2J_{gem}$ = 8.0 Hz, H, C**CH_2**); 6.37 (d, $^2J_{gem}$ = 8.0 Hz, H, C**CH_2**); 7.11 (t, ^3J = 8.0 Hz, H, **C^6H**); 7.22 (t, ^3J = 8.0 Hz, H, **C^5H**); 7.545 (d, ^3J = 8.0 Hz, H, **C^4H);** 8.08 (s, H, N**CH**); 8.46 (br, s, H, **C^7H**). ^{13}C NMR ($CDCl_3$, 100 MHz): 28.4 (OC**$(CH_3)_3$**); 31.0 (O**CH_3**); 52.5 (**CH_2**CO); 84.1 (O**C**$(CH_3)_3$); 115.6 - 149.4 (**C**Ph); 167.0 (CH_2**CO**). HRMS (ESI): calcd. for $C_{17}H_{19}NO_4[M]^+$: 301.3420, found: $C_{17}H_{20}NO_4$ [M + H^+]: 302.1398.

Methyl 2-(1-*Methyl*-1*H-Indol*-3-*yl*)*Acrylate* ***4c***.

According to General Procedure 3, 0.52 g (2.56 mmol) of **2c**, 0.512 g (12.79 mmol) of NaH 60% and 0.692 g (23.04 mmol) of paraformaldehyde were added. Green oil, yield 62%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 3.78 (s, 3H, N**CH_3**); 3.85 (s, 3H, O**CH_3**); 6.11 (d, $^2J_{gem}$ = 1.2 Hz, H, C**CH_2**); 6.34 (d, $^2J_{gem}$ = 1.2 Hz, H, C**CH_2**); 7.44 (m, 3H, **C^4H**-**C^5H**-**C^6H**); 7.49 (s, 1H, N**CH**); 7.76 (d, ^3J = 7.0 Hz, H, C^6H-**C^7H**). ($CDCl_3$, 100 MHz), δ (ppm): 33.1 (O**CH_3**); 52.3 (**CH_2**CO); 109.7 (**C-4**); 110.5 (**C-3**) 120.1 (**C-7**); 120.3 (**C-6**); 122.2 (**C-5**); 122.5 (C-**CH_2**); 126.6 (**C**-CH_2); 130.1 (**C-2**); 133.9 (**C_{ipso}-3a**); 137.2 (**C_{ipso}-7a**); 167.9 (CH_2**CO**).

Dimethyl 2,4-*Diphenylpentanedioate* **5**.

Isolated as a byproduct from **2a** reaction conditions such as is shown in Table 1, Entry 1. Colorless oil, yield 55%. Erythro and Threo mixture. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.57 (m, 2H, **CH_2**CH), 3.41 (m, 1H, **CH**CH_2), 3.60 (s,s, 6H, **CH_3**O), 7.27 (m, 10H, **Ph**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 36.7 (**CH_2**CH), 49.1 (**CH**CH_2), 52.3 (**CH_3**O), 127.8 (**C**Ph), 128.0 (**C**Ph), 128.9 (**C**Ph), 138.2 (C_{ipso}-**Ph**), 173.8 (**C**OOCH_3). HRMS: calcd. for $C_{19}H_{20}O_4[M]^+$: 312.1362, found: $C_{19}H_{20}O_4$: 312.3470.

Methyl 3-*Methoxy*-2-*Phenylpropanoate* ***6a***.

Isolated as byproduct from **2a** reaction conditions such as is shown in **Table 1**, Entry 7**.** Colourless oil, yield 29%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 3.36 (s, 3H, **CH_3**OCH_2), 3.57 (dd, J = 8.4 Hz, J = 4.4 Hz, 1H, **CH**Ph), 3.69 (s, 3H, **CH_3**OCO), 3.91 (dd, J = 9.6 Hz, J = 4.4 Hz, 1H, **CH_2**CH), 3.99 (dd, J = 9.4 Hz, J = 8.4 Hz, 1H, **CH_2**CH), 7.35 (m, 5H, **Ph**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.0 (**CH_3**OCH_2), 52.3 (**CH**Ph), 59.2 (**CH_3**OCO), 74.4 (**CH_2**CH), 127.8 (**C**Ph), 128.1 (**C**Ph), 128.8 (**C**Ph), 135.7 (C_{ipso}-**Ph**), 172.9 (**C**OOCH_3). HRMS: calcd. for $C_{11}H_{14}O_3[M]^+$: 194.0943, found: $C_{11}H_{14}O_3$: 194.0990.

Dimethyl 2-(*Methoxymethyl*)-2,4-*Diphenylpentanedioate* **7**.

Isolated as byproduct from **2a** reaction conditions such as is shown in **Table**

1, Entry 6. Colourless oil, yield 11%. Diastereomers and enantiomers mixture. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.80 (m, 2H, **CH_2**CH), 3.20 (s, 3H, **CH_3**OC), 3.35 (m, 1H, **CH**Ph), 3.45 (s, 3H, **CH_3**OCO), 3.83 (s, 3H, **CH_3**OCO), 3.90 (m, 2H, **CH_2**C), 7.25 (m, 10H, 2**Ph**). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 36.9 (**CH_2**CH), 50.0 (**CH**Ph), 52.8 (**CH_3**OCOCH), 53.2 (**CH_3**OCOC), 75.7 (**CH_2**C), 128.1 (C_{ipso}-Ph), 136.6 (**C**Ph), 141.0 (**C_{ipso}**-Ph), 174.3 (CH**C**(O)OCH_3), 177.4 (C**C**(O)OCH_3). HRMS: calcd. for $C_{21}H_{24}O_5[M]^+$: 356.1624, found: $C_{21}H_{24}O_5$ $[M + Na]^+$: 379.1517. X-Ray crystallographic structure in **Figure 1** [27].

Methyl 2-(1-((*Pivaloyloxy*)*methyl*)-1*H-Indol*-3-*yl*)*Acrylate* **8*d***.

According to General Procedure 3, 0.52 g (1.9 mmol) of **2d**, 0.38 g (9.5 mmol) of NaH 60% and 0.514 g (17.12 mmol) of paraformaldehyde were added. Green-yellow oil, yield 37%. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.14 (s, 9H, **$(CH_3)_3$**CO); 3.84 (s, 3H, O**CH_3**); 6.07 (s, 2H, N**CH_2**O); 6.13 (d, $^2J_{gem}$ = 1.2 Hz, H, C**CH_2**); 6.41 (d, $^2J_{gem}$ = 1.2 Hz, H, C**CH_2**); 7.21 (td, $^3J_1$ = 1.2 Hz, $^3J_2$ = 7.2 Hz, H, **C^6H**); 7.28 (td, $^3J_1$ = 1.2 Hz, $^3J_2$ = 7.2 Hz, H, **C^5H**); 7.49 (d, ^3J = 8.4 Hz, H, **C^4H**); 7.64 (s, H, N**CH**); 7.72 (d, ^3J = 8.0 Hz, H, **C^7H**). ^{13}C NMR ($CDCl_3$ 100 MHz), δ (ppm): 26.9 (OC**$(CH_3)_3$**); 38.9 (O**C**$(CH_3)_3$); 52.1 (O**CH_3**); 68.7 (N**CH_2**O); 109.9 (**C-4**); 112.9 (**C-3**) 120.1 (**C-7**); 121.2 (**C-6**); 122.8 (**C-5**); 123.9 (C-**CH_2**); 127.1 (**C**-CH_2); 129.3 (**C-2**); 133.4 (**C_{ipso}-3a**); 136.4 (**C_{ipso}-7a**); 167.4 (($CH_3)_3$**CO**); 178.0 (CH_2C**CO**). HRMS (FAB+): calcd. for $C_{18}H_{21}NO_4[M]^+$: 315.3690, found: $C_{17}H_{20}NO_4$ $[M + H^+]$: 316.1537.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Yamago, S., Iida, K. and Yoshida, J.-I. (2002) Tailored Synthesis of Structurally Defined Polymers by Organotellurium-Mediated Living Radical Polymerization (TERP): Synthesis of Poly(meth)acrylate Derivatives and Their Di- and Triblock Copolymers. *Journal of the American Chemical Society*, **124**, 13666-13667. https://doi.org/10.1021/ja027599i

[2] Pignatello, R., Bucolo, C., Spedalieri, G., Maltese, A. and Puglisi, G. (2002) Flurbiprofen-Loaded Acrylate Polymer Nanosuspensions for Ophthalmic Application. *Biomaterials*, **23**, 3247-3255. https://doi.org/10.1016/S0142-9612(02)00080-7

[3] Nguyen, L.H., Straub, M. and Gu, M. (2005) Acrylate-Based Photopolymer for Two-Photon Microfabrication and Photonic Applications. *Advanced Functional Materials*, **15**, 209-216. https://doi.org/10.1002/adfm.200400212

[4] Metz, N. and Theato, P. (2007) Controlled Synthesis of poly(acetone oxime acrylate) as a New Reactive Polymer: Stimuli-Responsive Reactive. *European Polymer Journal*, **43**, 1202-1209. https://doi.org/10.1016/j.eurpolymj.2007.01.009

[5] Kiyota, H., Takai, T., Saitoh, M., Nakayama, O., Takayuki, O. and Kuwahara, S. (2004) Facile Synthesis of (-)-tabtoxinine-*β*-lactam and Its (3'*R*)-Isomer. *Tetrahedron Letters*, **45**, 8191-8194. https://doi.org/10.1016/j.tetlet.2004.09.033

[6] Erkkilä, A., Majander, I. and Pihko, P. (2007) Iminium Catalysis. *Chemical Reviews*, **107**, 5416-5470. https://doi.org/10.1021/cr068388p

[7] Shi, Y. and Shi, M. (2007) Aza-Baylis-Hillman Reactions and Their Synthetic Applications. *European Journal of Organic Chemistry*, 2905-2916. https://doi.org/10.1002/ejoc.200700030

[8] Fernandes, L., Bortoluzzi, A.J. and Sá, M.M. (2004) Simple Access to 2-Methylalk-2-Enoates and Insect Pheromones by Zinc-Promoted Reduction of Baylis-Hillman-Derived Allylic Bromides. *Tetrahedron*, **60**, 9983-9989. https://doi.org/10.1016/j.tet.2004.08.018

[9] An, L.-T., Zou, J.-P. and Zhang, L.-L. (2008) Polymer-Supported Sulphonic Acid Catalyzed Cross-Aldol Condensation: An Expeditious Synthesis of *α*, *α*'-bis(substituted Benzylidene) Cycloalkanones. *Catalysis Communications*, **9**, 349-354. https://doi.org/10.1016/j.catcom.2007.06.004

[10] Sarkar, B.R. and Chaudhari, R.V. (2005) Carbonylation of Alkynes, Alkenes, and Alcohols Using Metal Complex Catalysts. *Catalysis Surveys from Asia*, **9**, 193-205. https://doi.org/10.1007/s10563-005-7556-x

[11] Hon, Y.-S., Liu, Y.-W. and Hsieh, C.-H. (2004) Dibromomethane as One-Carbon Source in Organic Synthesis: A Versatile Methodology to Prepare the Cyclic and Acyclic Methylene or *α*-Keto Acid Derivatives from the Corresponding Terminal Alkenes. *Tetrahedron*, **60**, 4837-4860. https://doi.org/10.1016/j.tet.2004.04.013

[12] Erkkilä, A. and Pihko, P.M. (2006) Mild Organocatalytic-Methylenation of Aldehydes. *Journal of Organic Chemistry*, **71**, 2538-2541. https://doi.org/10.1021/jo052529q

[13] Bugarin, A., Jones, K.D. and Connell, B.T. (2010) Efficient, Direct *α*-Methylenation of Carbonyls Mediated by Diisopropylammonium Trifluoroacetate. *Chemical Communications*, **10**, 1715-1717. https://doi.org/10.1039/b924577d

[14] Giguère, D., Cloutier, P. and Roy, R. (2009) Domino Heck/Lactonization-Catalyzed Synthesis of 3-*C*-Linked Mannopyranosyl Coumarins. *Journal of Organic Chemistry*, **74**, 8480-8483. https://doi.org/10.1021/jo901855p

[15] Mandal, S., Mandal, S., Ghosh, S.K., Ghosh, A., Saha, R., Banerjee, S. and Saha, B. (2016) Review of the Aldol Reaction. *Synthetic Communications*, **46**, 1327-1342. https://doi.org/10.1080/00397911.2016.1206938

[16] Machajewski, T.D. and Wong, C.-H. (2000) The Catalytic Asymmetric Aldol Reaction. *Angewandte Chemie International Edition*, **39**, 1352-1374. https://doi.org/10.1002/(SICI)1521-3773(20000417)39:8<1352::AID-ANIE1352>3.0.CO;2-J

[17] Wang, J., Lei, M., Li, Q., Ge, Z., Wang, X. and Li, R. (2009) A Novel and Efficient Direct Aldol Condensation from Ketones and Aldehydes Catalyzed by Proline-TEA through a New Pathway. *Tetrahedron*, **65**, 4826-4833. https://doi.org/10.1016/j.tet.2009.04.052

[18] Hora, L., Kelbichová, V., Kikhtyanin, O., Bortnovskiy, O. and Kubička, D. (2014) Aldol Condensation of Furfural and Acetone over Mg-Al Layered Doublé Hydroxides and Mixed Oxides. *Catalysis Today*, **223**, 138-147. https://doi.org/10.1016/j.cattod.2013.09.022

[19] Habib-Zahmani, H., Hacini, S., Bories, C., Faure, R. and Rodriguez, J. (2005) An Operationally Simple Base-Catalyzed Multi-Component Domino Transformation:

Stereoselective Preparation on Trisubstituted Alkenes and 1,3-Dienes. *Synthesis*, **36**, 2151-2156.

[20] Laos, I. (1967) Direct Methylenation of Steroidal *α*,*β*-Epoxy Ketones. *Journal of Organic Chemistry*, **32**, 1409-1413. https://doi.org/10.1021/jo01280a026

[21] Ma, Z., Ma, X., Ni, Y., Liu, H., Zhu, W., Guo, X. and Liu, Z. (2018) HZSM-35 Zeolite Catalyzed Aldol Condensation Reaction to Prepare Acrylic Acid and Its Ester: Effect of Its Acidic Property. *Chinese Journal of Catalysis*, **39**, 1762-1769. https://doi.org/10.1016/S1872-2067(18)63145-6

[22] Samarat, A., Fargeas, V., Villiéras, J., Lebreton, J. and Amri, H. (2001) A New Synthesis of (±)-Homosarkomycin Ethyl Ester. *Tetrahedron Letters*, **42**, 1273-1274. https://doi.org/10.1016/S0040-4039(00)02238-3

[23] Tanaka, A. and Yamashita, K. (1978) A Simple Procedure for *α*-Methylenation or *γ*- and *δ*-Lactones. *Agricultural and Biological Chemistry*, **42**, 1585-1588. https://doi.org/10.1080/00021369.1978.10863208

[24] Sui, Y., Liu, L., Zhao, J.-L., Wang, D. and Chen, Y.-J. (2007) An Efficient One-Pot Reaction of Indoles, Nitroacetates, and Paraformaldehyde for the Synthesis of Tryptophan Derivatives. *Tetrahedron Letters*, **48**, 3779-3782. https://doi.org/10.1016/j.tetlet.2007.04.002

[25] Rangel, H., Carrillo-Morales, M., Galindo, J.M., Castillo, E., Obregón-Zúñiga, A., Juaristi, E. and Escalante, J. (2015) Structural Features of *N*-Benzylated-*β*-Amino Acid Methyl Esters Essential for Enantio Differentiation by LIPASE B from Candida Antarctica in Hydrolytic Reactions. *Tetrahedron*: *Asymmetry*, **26**, 325-332. https://doi.org/10.1016/j.tetasy.2015.02.007

[26] Crystallographic Data Is Deposited at Cambridge Crystallographic Data Center CCDC: No. 1877662.

[27] Crystallographic Data Is Deposited at Cambridge Crystallographic Data Center CCDC: No. 1876262.