

Ultrasound-accelerated arylthiomethylation of indole via multicomponent reaction in water catalyzed by acetic acid

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(Received on June 5th 2016, accepted on April 10th 2017)

ABSTRACT

Multicomponent reactions (MCRs) play an important role to create the molecular complexity in a one-step process. Based on the mechanism and process of Mannich-type reactions in the synthesis of Grammin, arylthiomethylation reactions of indole were performed by using three components: indole,

p-thiocresol and a solution of formaldehyde (36%) under two activation conditions, e.g. magnetic stirring and ultrasonic irradiation. The main product, 3-(*p*-tolylthiomethyl)-1*H*-indole, was obtained in a moderate yield (54%) under short irradiation (40 minutes) by probe sonicator.

Keywords: arylthiomethylation, ultrasound irradiation, acetic acid, and indole

INTRODUCTION

Mannich reaction classified into multicomponent reactions (MCRs), has been fairly extensively investigated, while there are few studies using thiols in place of amines for Mannich-type reaction, namely alkylthiomethylation and arylthiomethylation. The latter has been used widely in organic chemistry, especially in total synthesis of natural products, e.g. sesquiterpenes and antibiotics [1-5].

Formaldehyde is a very active substrate frequently used in three-component reactions in order to generate active methylene transition compounds (or methides) via the methylenation of electron-rich carbons with formaldehyde. Subsequently, these active methylene intermediates were trapped by α,β -unsaturated ketones [1], α,β -unsaturated esters [2],

lactams [3, 4, 6], thiols [5, 7], indole [7, 8], and polyarenes [9].

In pursuit of our work on the analogue of the Mannich reaction, we report the arylthiomethylation involving indole, *p*-thiocresol and the solution of formaldehyde (36 %) to produce 3-(*p*-tolylthiomethyl)-1*H*-indole under the assistance of ultrasound irradiation in comparison with the one under magnetic stirring (Fig. 1). According to our literature review on the three-component reaction of indole, alkanethiol/arenethiol and formaldehyde, it was found that only one article described the yield around 25 % of desired products obtained for six-day magnetic stirring [8].

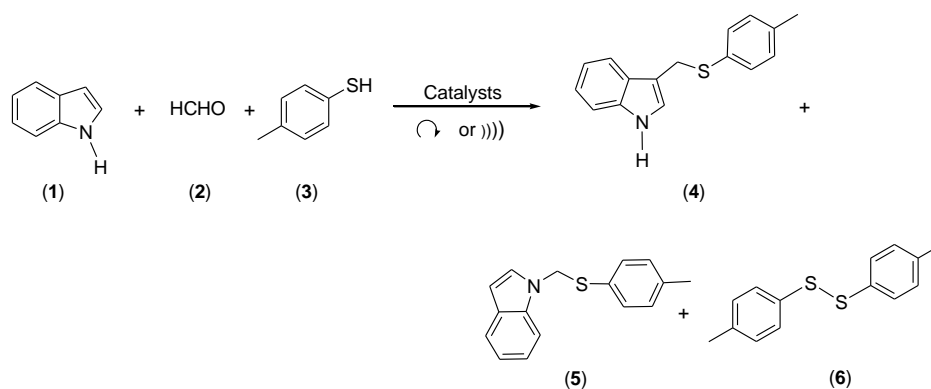


Fig. 1. Phenylthiomethylation involving indole, (1) *p*-thiocresol (3) and the solution of formaldehyde (2) to afford 3-(*p*-tolylthiomethyl)-1*H*-indole

MATERIALS AND METHODS

Instrumentation

Ultrasonic irradiation was performed by means of a probe sonicator GE130-41505L with 1/8" (3 mm) stepped microtip, operating at frequency 20 kHz. GC/MS analyses were performed on Agilent 7890A apparatus equipped with HP 5MS capillary column (30 m x 250 μm x 0.25 μm) and 5973C VL MSD with Triple-Axis Detector, detector and injector temperature at 250 $^{\circ}\text{C}$, gas carrier (Helium) at 11.104 mL/min (total flow), and oven temperature programme as follows: started at initial temperature is 50 $^{\circ}\text{C}$ (maintained 2 min), increased 10 $^{\circ}\text{C}/\text{min}$ up to 300 $^{\circ}\text{C}$ (maintained 4 min). GC analyses were performed on Agilent 6890N apparatus equipped with capillary column (30 m x 320 μm x 0.25 μm), detector and injector temperature at 250 $^{\circ}\text{C}$, gas carrier (Nitrogen) at 1.0 mL/min (total flow), and oven temperature programme as follows: started at initial temperature is 80 $^{\circ}\text{C}$ (maintained 1 min), increased 25 $^{\circ}\text{C}/\text{min}$ up to 230 $^{\circ}\text{C}$ (maintained 1 min) and continued increasing up to 300 $^{\circ}\text{C}$ (maintained 2 min). NMR spectra were recorded on Bruker 500 NMR spectrometer at 500 MHz (^1H) and 125 MHz (^{13}C).

Chemicals

All commercially available chemicals used were purchased from Aldrich and analyzed for authenticity and purity by GC/MS prior to use.

General procedure of arylthiomethylation of indole with *p*-thiocresol and the solution of formaldehyde (36 %) into 3-(*p*-tolylthiomethyl)-1*H*-indole under ultrasound irradiation

p-Thiocresol (0.248 g, 2.0 mmol) was added into the 25 mL two-neck pear flask containing 6 mL of water, then glacial acetic acid (0.180 g, 3 mmol), the formaldehyde (2.0 mmol, 36 % aq.) and the indole (0.351 g, 3.0 mmol) were added successively. The flask was equipped with the ultrasound probe and irradiated at a suitable amplitude for a specific period of time. Subsequently, 7 mL of water was added and the pH was adjusted to pH 11–13 by 20 % NaOH solution. The reaction mixture was extracted with dichloromethane (4 x 15 mL). The combined extracts were washed with water until pH 8, and then dried (anhydrous Na_2SO_4). After removal of the solvent by rotatory evaporation, the crude product was analysed by GC or GC/MS. The product was isolated by flash column chromatography (4–7 g silica gel, Davisil, grade 710, 4–20 μm , 60 A, 99 %) using as eluent a mixture of hexane and ethyl acetate (9:1 v/v).

Spectroscopic data

The identity and purity of products reported were ensured by GC/MS and NMR spectroscopy as descriptions below:

3-(*p*-Tolylthiomethyl)-1*H*-indole (4), C₁₆H₁₅NS (M = 253), white solid, mp 145-146 °C. ¹H NMR (500 MHz, CDCl₃) δ_H = 7.53 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.0 Hz, 1H), 7.19 (t, *J* = 7.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 6.54 (s, 1H), 5.31 (s, 2H), 2.27 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ_C = 138.6, 136.3, 134.3 (2C), 130.1, 129.9 (2C), 129.0, 126.0, 121.9, 119.6, 119.5, 115.4, 110.1, 29.9, 21.3. MS (EI, 70 eV): *m/z* = 253[M]⁺, 162, 130, 118, 103, 91, 77.

N-(*p*-Tolylthiomethyl)indole (5), C₁₆H₁₅NS (M = 253), white solid, mp 130–132 °C. ¹H NMR (500 MHz, CDCl₃) δ_H = 7.60 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.0 Hz, *J* = 0.5 Hz, 1H), 7.18 (td, *J* = 8.0 Hz, *J* = 1 Hz, 1H), 7.10-7.13 (m, 3H), 7.03 (d, *J* = 8.0 Hz, 2H), 6.81 (d, *J* = 3 Hz, 1H), 6.40 (dd, *J* = 3.0 Hz, *J* = 0.5 Hz, 1H), 5.39 (s, 2H) 2.31 (s, 3H). ¹³C NMR (125 MHz, CDCl₃): δ_C = 139.1, 134.6 (2C), 130.3(2C), 130.2, 130.1, 129.6, 128.2, 122.2, 121.4, 120.4, 110.4, 102.7, 53.0, 21.5. MS (EI, 70 eV): *m/z* = 253[M]⁺, 162, 130, 118, 103, 91, 77.

RESULTS AND DISCUSSION

At the beginning of this work, the reactions of indole, *p*-thiocresol and the solution of formaldehyde without using catalyst were performed under magnetic stirring for 2.5 h. The results showed that the three-component reactions in the absence of the catalyst did not take place. This led us to test several catalysts such as CH₃COOH, NiCl₂·6H₂O, Mg-Al Hydrotalcite, and KF/Al₂O₃ (wt. 40 %) for this arylthiomethylation. Consequently, it was noticeable that acetic acid played a crucial role in our multicomponent reaction (Table 1).

A series of experiments with different molar ratios between *p*-thiocresol and acetic acid, as well as *p*-thiocresol and indole, was carried out to improve the reaction yield (Entries 1–5, Table 2). The optimum yield was observed when 3.0 mmol of acetic acid was utilized as catalyst; whereas the excessive amount of this acidic catalyst led to a remarkable reduction of product yield owing to the deactivation of indole ring from the protonation of nitrogen atom under acidic media.

Table 1. Effect of the catalyst nature on the arylthiomethylation of indole with *p*-thiocresol and the solution of formaldehyde^a

Entry	Catalyst (mmol)	GC (%)					Yield ^b (%)
		1	3	4	5	6	
1	None	50.87	42.79	1.21	0	0	1
2	CH ₃ COOH	0	17.76	48.77	0	33.47	47
3	NiCl ₂ ·6H ₂ O	85.63	2.41	2.20	0	1.92	2
4	Mg-Al Hydrotalcite	4.49	91.39	0.95	1.25	1.92	0.6
5	KF/Al ₂ O ₃ wt. 40 %	4.08	62.87	4.18	5.61	5.64	4

^a The reactions of *p*-thiocresol (2.0 mmol) and indole (2.0 mmol) with the solution of formaldehyde 36 % (2.0 mmol) in the presence of catalyst (3.0 mmol) were performed under magnetic stirring at room temperature for 2.5 h.

^b Yields were calculated based on GC-FID analysis.

Table 2. Influence of reaction conditions on the yield of 3-(*p*-tolylthiomethyl)-1*H*-indole^a

Entry	Indole (mmol)	CH ₃ COOH (mmol)	Time (h)	Yield ^b (%)
1	2.0	1.5	2.5	29
2	2.0	3.0	2.5	43
3	2.0	4.5	2.5	37
4	3.0	3.0	2.5	51
5	4.0	3.0	2.5	47
6	3.0	3.0	1.5	10
7	3.0	3.0	3.5	53
8	3.0	3.0	24	45
9 ^c	3.0	3.0	30 min	16
10 ^c	3.0	3.0	40 min	54
11 ^c	3.0	3.0	50 min	41
12 ^c	3.0	3.0	60 min	36

^a The reactions with a fixed amount of formaldehyde (2.0 mmol) and *p*-thiocresol (2.0 mmol) were conducted by magnetic stirring at room temperature.

^b Yields were calculated based on GC-FID analyses.

^c The reactions with a fixed amount of formaldehyde (2.0 mmol) and *p*-thiocresol (2.0 mmol) were assisted by probe sonicator with amplitude at 64 micrometer.

In the next step, the reaction time was investigated under two activation methods. In the first series of arylthiomethylation of indole, the mixture of reactants were allowed to react under magnetic stirring for 1.5 h, 2.5 h, 3.5 h and 24 h at room temperature (Entries 4, 6–8, Table 2). In the second series, some reactions performed under the ultrasound

irradiation were compared with those above (Entries 9-12, Table 2). We first investigated the effect of ultrasonic amplitudes at 48 μm, 64 μm, 80 μm, 96 μm, and 128 μm on the yield of desired indole. The results demonstrated that the most efficient amplitude to accelerate this reaction was at 64 μm (Fig. 2).

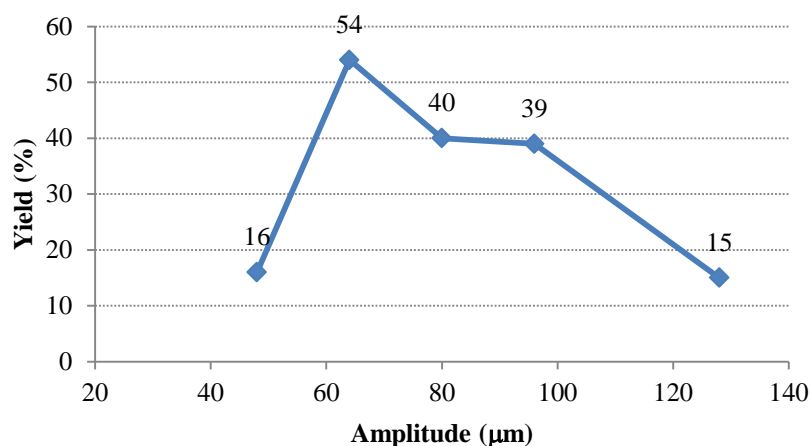


Fig. 2. Influence of amplitude on the efficiency of arylthiomethylation of indole to generate the 3-(*p*-tolylthiomethyl)-1*H*-indole under ultrasonic irradiation for 40 min (indole: 3.0 mmol, *p*-thiocresol: 2.0 mmol and formaldehyde: 2.0 mmol)

The comparison of the experiments activated by two methods showed that a maximum yield of 4 obtained by the three-component reaction with acetic acid as catalyst reached 54 % after forty-minute ultrasound irradiation, while it was 53 % after three and half hour magnetic stirring. It could be explained that the disruption of the phase boundary, owing to a formation of extremely fine emulsions from the mixture of immiscible liquids under ultrasonic irradiation, increased the interfacial contact area between the reactant layers [10].

CONCLUSION

In summary, we have successfully developed an efficient and mild synthetic protocol of 3-(*p*-tolylthiomethyl)-1*H*-indole via three-component reaction of indole, *p*-thiocresol and the solution of formaldehyde (36 %) in the presence of acetic acid as catalyst. Ultrasound irradiation has influenced significantly on the reduction of the reaction time without any loss of product yield in comparison with magnetic stirring.

Bức xạ siêu âm xúc tiến sự arylthiometyl hóa indol qua phản ứng đa thành phần trong môi trường nước dưới sự xúc tác của acetic acid

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TÓM TẮT

Phản ứng đa thành phần (MCRs) đóng vai trò quan trọng để tạo ra các phân tử phức tạp theo quy

trình phản ứng một bước. Dựa trên cơ chế và quy trình phản ứng Mannich trong sự điều chế Grammin,

sự arylthiomethyl hóa của indol được thực hiện với ba chất phản ứng: indol, *p*-thiocresol và dung dịch formaldehyd (36 %) dưới hai phương pháp kích hoạt như khuấy từ và siêu âm. Sản phẩm chính 3-(*p*-

tolythiomethyl)-1*H*-indol thu được với hiệu suất khá cao (54 %) trong thời gian ngắn (40 phút) dưới sự kích hoạt của thanh siêu âm.

Từ khóa: arylthiomethyl hóa, bức xạ siêu âm, acetic acid và indol

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