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Uncatalyzed Michael addition of indoles: synthesis of some novel 3-alkylated indoles via a three-component reaction in solvent-free conditions

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Abstract—Synthesis of some novel 3-alkylated indoles via an uncatalyzed Michael addition of indoles using three components in one-pot solvent-free conditions is reported. The mechanism was established by performing the reaction in two steps. The reaction was also studied in different solvents and an important solvent effect was noticed.

The importance of indoles is well recognized by synthetic as well as biological chemists.[1] The most ubiquitous of the known bioactive alkaloids are based on the indole moiety.[2] Medicinal chemists repeatedly turn to indole-based compounds as a target pharmacophore for the development of therapeutic agents.[3] The prevalence of this motif in natural and bioactive products continues to be a vector in the development of new methodology to find useful compounds.[4] Michael addition of indoles to α,β-unsaturated systems is an efficient approach to indole-containing molelcules.[5] Owing to the total atom efficiency these reactions are inherently green.[6] The regioselectivity in the addition of indoles to electron-deficient alkenes is strongly controlled by the reaction conditions: N-alkylation under alkaline conditions and C-3-substitution in acid-catalyzed reactions. Besides protic acids, a number of Lewis acid catalyzed methodologies for the C-3 alkylation of indoles by Michael addition have been reported[7] and the use of lanthanide triflates[8] represents an attractive alternative to their classical competitors such as $AlCl_3$ and $SnCl_4$. Unfortunately, lanthanide triflates are rather expensive and their use in large-scale synthetic methodology is very limited. Recently $CeCl_3{\cdot}7H_2O$–NaI supported on silica gel was successfully utilized for the Michael addition of indoles to an α,β-unsaturated system.[9]

Barbituric acids are an important class of compounds that constitute the basic moiety of a number of clinically used hypnotic drugs of the barbiturate class (5-alkylated barbituric acids), for example, Veronal, Seconal, Phenobarbital and Luminal.[10]

Development of new solid-phase (solvent-free) reactions and transferring solution-phase reactions to solid-phase are subjects of recent interest in the context of generating libraries of molecules for the discovery of biologically active leads and also for the optimization of drug candidates.[11] One-pot multi-component reactions (MCRs), by virtue of their convergence, ease of execution and generally high yields of products have attracted considerable attention.[12] In the past decade there have been tremendous developments in three- and four-component reactions and great efforts have been and continue to be made to find and develop new MCRs.[13]

In our continued interest in the synthesis of diverse heterocyclic compounds of biological importance,[14] we report here the synthesis of some novel 3-alkylated indoles via a three-component reaction in solvent-free conditions. The reaction, which gave access to 5-alkylated barbituric acids also demonstrated an uncatalyzed Michael addition of indoles to an α,β-unsaturated system (Scheme 1).

Utilizing equimolar amounts of indole **1a** benzaldehyde **2a** and *N*,*N*-dimethylbarbituric acid **3a** in the absence of solvents at 95 °C for 15 min afforded[15] after work-up,

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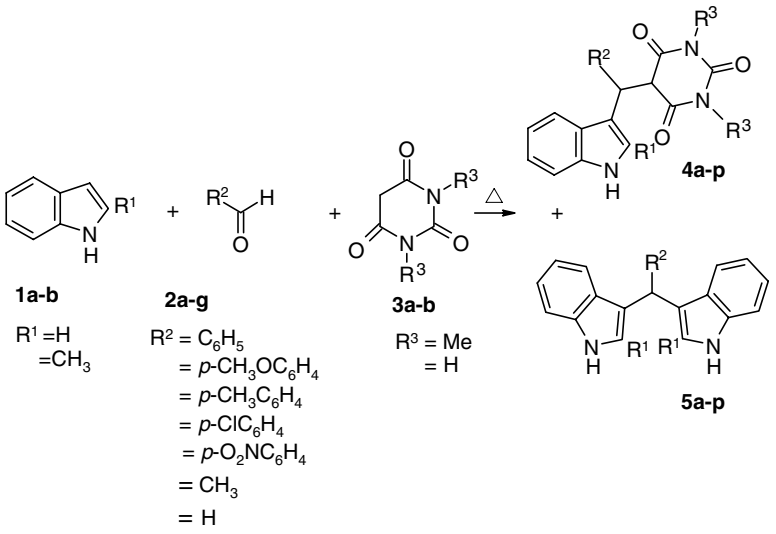


Scheme 1.

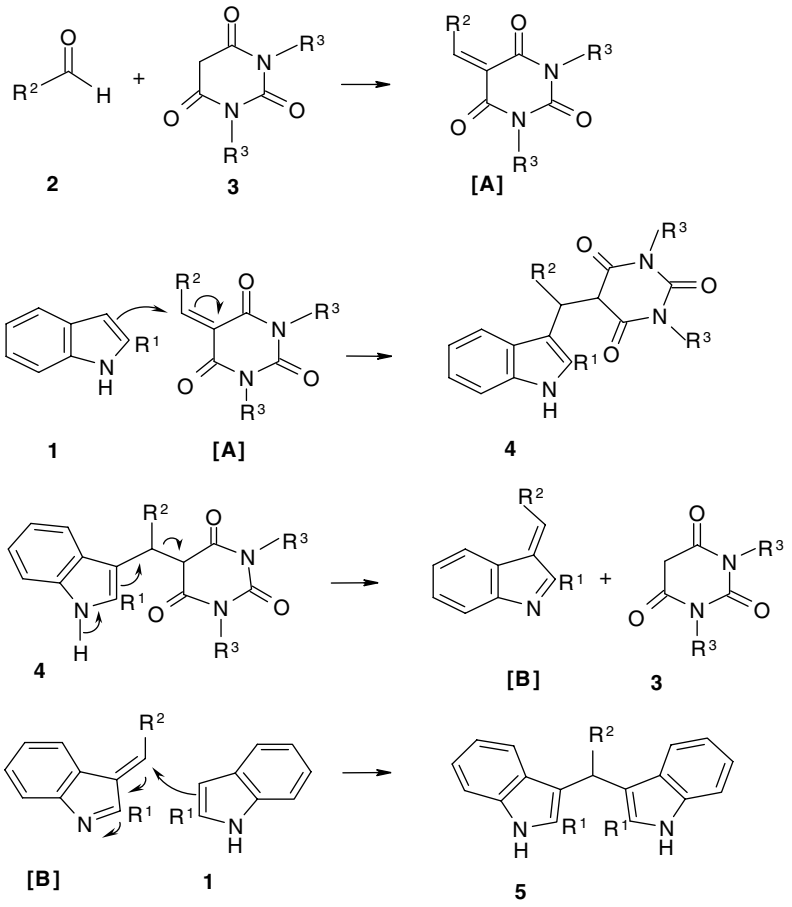
67% of 3-alkylated indole **4a** as a crystalline compound, the structure confirmed from the spectroscopic data and elemental analysis. In addition to the Michael adduct, we isolated 15% of 3,3′-bisindolylmethane **5a**, with physical and spectroscopic data comparable in all respects to those of an authentic sample.[16] Similarly compounds **4b**–**p** and **5b**–**p** were synthesized from **1**–**3** and characterized. The reaction is equally applicable to aliphatic aldehydes. The three-component reactions and our observations are recorded in Table 1. 2-Methylindole was found to be highly reactive and the formation of compounds **4** and **5** to depend on the reaction time. Thus, we obtained a maximum yield of compound **4** in 10 min, while a reaction time above 15 min maximized the yield of bisindolylmethanes **5**. However, we obtained **4** as a minor compound and **5** as a major compound when **3b** was utilized in the three-component reactions.

A reasonable mechanism for the formation of 3-alkylated indoles from the three-component reaction is outlined in Scheme 2. The sequence starts with the formation of Knoevenagel product [**A**] from **2** and **3** under thermal condition which then suffers a nucleophilic attack by indole **1** to give Michael adduct **4**. The formation of minor bisindolylmethane **5** can be explained by the formation of small amount of [**B**] from product **4** with the elimination of barbituric acid **3** under thermal conditions.[17] The intermediate [**B**] then adds a second indole to give **5**. Comparatively easy formation of intermediate [**B**] might be the reason for small yields of the compounds **4n**–**p** and hence the maximum formation of bisindolylmethanes **5n**–**p**.

We confirmed the mechanism by performing the transformations in two steps. First we synthesized the α,β-unsaturated system [**A**] by condensing aldehydes **2** with barbituric acids **3** following our own method[18] and then reacted [**A**] with indole at 85 °C for 10–25 min in the absence of solvent.[19] As expected we obtained 3-alkylated indoles **4** as a major product and bisindolylalkanes **5** as a minor product (Table 2). The small amounts of barbituric acids **3** eliminated during the process were isolated and characterized. However,

Table 1. Three-component reactions of **1**–**3** in solvent-free conditions and synthesis of 3-alkylated indoles **4** and bisindolylmethanes **5**

R^1 of **1**	R^2 of **2**	R^3	Time (min)	Temperature (°C)	Product **4**	Yield (%)	Product **5**	Yield (%)
H	C_6H_5	CH_3	15	95	**4a**	67	**5a**	15
H	4-MeC_6H_4	CH_3	15	85	**4b**	65	**5b**	12
H	4-$MeOC_6H_4$	CH_3	15	85	**4c**	68	**5c**	10
H	4-ClC_6H_4	CH_3	15	85	**4d**	61	**5d**	14
H	4-$O_2NC_6H_4$	CH_3	15	110	**4e**	70	**5e**	12
CH_3	C_6H_5	CH_3	12	80	**4f**	73	**5f**	10
CH_3	4-MeC_6H_4	CH_3	10	80	**4g**	70	**5g**	12
CH_3	4-$MeOC_6H_4$	CH_3	10	80	**4h**	74	**5h**	10
CH_3	4-ClC_6H_4	CH_3	15	80	**4i**	74	**5i**	10
CH_3	4-O_2N–C_6H_4	CH_3	15	80	**4j**	74	**5j**	11
H	CH_3	CH_3	25	80	**4k**	64	**5k**	15
H	H	CH_3	25	100	**4l**	74	**5l**	10
CH_3	H	CH_3	20	120	**4m**	75	**5m**	8
H	C_6H_5	H	25	120	**4n**	22	**5a**	59
CH_3	C_6H_5	H	25	150	**4o**	24	**5f**	65
H	4-MeC_6H_4	H	25	150	**4p**	23	**5b**	62
				150				



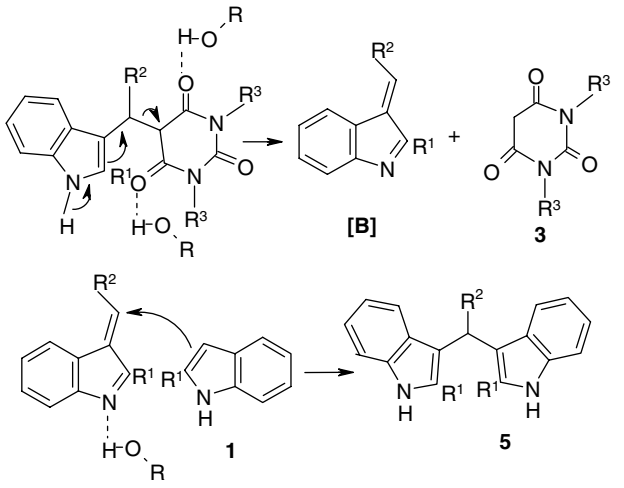
Scheme 2.

Table 2. Two-component reactions of **1** & [**A**] in solvent-free/in solvent (acetonitrile) and synthesis **4** and **5**

Entry	Solvent free/(in solvent) Time (min/h), Temperature (°C)	Product **4**	mp (°C)	Yield (%)	Product **5**	Yield (%)
1	15 min, 85 (11 h), (rt)	**4a**	175–176	65 (64)	**5a**	10 (8)
2	15 min, 85 (11 h), (rt)	**4b**	156–158	72 (75)	**5b**	7 (5)
3	15 min, 85 (10 h), (rt)	**4c**	171–173	74 (71)	**5c**	5 (4)
4	15 min, 85 (11 h), (rt)	**4d**	161–162	70 (70)	**5d**	8 (5)
5	15 min, 80 (9 h), (rt)	**4e**	148–150	65 (70)	**5e**	11 (7)
6	5 min, 80 (9 h), (rt)	**4f**	177–178	70 (72)	**5f**	10 (8)
7	5 min, 80 (9 h), (rt)	**4g**	171–173	72 (70)	**5g**	10 (7)
8	7 min, 80 (9 h), (rt)	**4h**	103–106	68 (72)	**5h**	12 (5)
9	8 min, 85 (10 h), (rt)	**4i**	179–181	68 (70)	**5i**	12 (10)
10	5 min, 85 (10 h), (rt)	**4j**	189–190	55 (52)	**5j**	20 (12)
11	40 min, 85 (13 h), (rt)	**4k**	163–164	63 (65)	**5k**	8 (5)
12	30 min, 85 (9 h), (rt)	**4l**	175–176	74 (75)	**5l**	—
13	30 min, 85 (9 h), (rt)	**4m**	173–174	67 (72)	**5m**	—
14	40 min, 85 (13 h), (rt)	**4n**	163–164	23 (22)	**5a**	60 (55)
15	30 min, 85 (9 h), (rt)	**4o**	175–176	26 (19)	**5f**	69 (62)
16	30 min, 85 (9 h), (rt)	**4p**	173–174	21 (20)	**5b**	58 (55)

in the case of formaldehyde, 3-alkylated indoles were obtained as the sole product. The reason is that unlike aromatic and aliphatic aldehydes containing an α-hydrogen, the intermediate is not stabilized by either resonance or hyperconjugation.

The reaction was now studied in acetonitrile, dioxane, methanol and ethanol, and in all the cases the desired compounds **4** were not formed even under refluxing conditions. However, in protic solvents we observed the formation of bisindolyl-methanes **5** as the sole products, which can be reasonably explained by our recent study.[14b] We also studied the two-component reactions in various solvents. Accordingly, when equimolar amounts of indoles and intermediates [**A**] were reacted in acetonitrile at room temperature for 9–13 h, we obtained (19–75%) of the Michael addition products **4** and (4–62%) of bisindolylmethanes **5**, while in refluxing



Scheme 3.

acetonitrile these reactions required 1 h to give similar results (Table 2).[20] As in the three-component reactions, in entries 14–16 we obtained **4** as minor and **5** as major products. However, in EtOH or MeOH, we obtained bisindolylmethanes **5** as major products (70–75%) and Michael adducts **4** as minor compounds, as rationalized by the mechanism shown in Scheme 3. The protic solvents help the elimination of **3** and thus enhance the formation of intermediate [**B**]. This was further confirmed by refluxing Michael adduct **4** with an equimolar amount of indole **1** in MeOH for 0.5 h which afforded 80% of bisindolyl methane **5**. In the case of formaldehyde, when the Michael adduct and indole were heated in methanol, bisindolylmethane was not formed. Thus, the non-formation of intermediate [**A**] in the three-component reactions in different solvents is the reason for the non-formation of product **4**.

In conclusion we have reported the synthesis of some novel 3-alkylated indoles via three-component reactions in solvent-free conditions. Moreover, the results demonstrated a novel uncatalyzed Michael addition of indoles to an α,β-unsaturated system in a one-pot three-component reaction under solvent-free conditions. The mechanism of the three-component reaction was established by synthesizing the proposed intermediate and by performing the overall transformation in two steps.

Acknowledgements

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15. An equimolar amount indole **1a** (117 mg, 1 mmol), benzaldehyde **2a** (106 mg, 1 mmol) and *N*,*N*-dimethylbar-

bituric acid **3a** (156 mg, 1 mmol) were heated at 95 °C for 15 min. The reaction mixture was cooled to rt and petroleum ether:ethanol (4:1) (5 ml) added. After few minutes a solid appeared and was filtered off and recrystallized from ethanol:chloroform (3:1) (241 mg, 67%) m.p = 175–176 °C. IR (KBr): 3436 (NH stretch), 3148 (w), 3048 (w), 2956 (w), 1748 (w), 1693 (s), 1677 (s), 1665 (s), 1378 (m), 740 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3 + CD_3COCD_3$) δ 3.00 (s, 3H, NMe), 3.11 (s, 3H, NMe), 4.36 (d, 1H, $J = 2.85$ Hz), 5.24 (d, 1H, $J = 2.7$ Hz), 6.98–7.41 (m, 10H), 8.21 (s, 1H, NH). ^{13}C NMR (75 MHz, $CDCl_3 + CD_3COCD_3$) δ 28.6, 28.7, 48.8, 55.0, 111.6, 114.6, 119.5, 120.0, 122.7, 124.2, 126.9, 128.3, 128.4, 128.8, 136.5, 138.8, 151.4, 168.2, 169.2: *m/z* 362 $(M+H)^+$. Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.80; H, 5.26; N, 11.63. Found: C, 70.25; H, 5.17; N, 11.52.

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19. Equimolar amounts of indole **1a** (117 mg, 1 mmol) and [**A**] (244 mg, 1 mmol) were mixed till homogeneous and heated at 85 °C for 15 min. The reaction mixture was cooled to rt and added petroleum ether:chloroform (4:1) (5 ml). The solid obtained was filtered off and recrystallized from a mixture of ethanol:chloroform (3:1). The compound was identified as **4a** from the spectroscopic data and elemental analysis. Yield = 234 mg (65%). The filtrate was evaporated to dryness and bisindolylmethane **5a** isolated from the residue by column chromatography on silica gel column (eluent:hexane) and characterized.
20. Equimolar amounts of indole **1a** (117 mg, 1 mmol) and [**A**] (244 mg, 1 mmol) in acetonitrile (15 ml) were stirred for 11 h (or refluxed for 1 h). The solvent was removed under reduced pressure and added petroleum ether:chloroform (4:1) (5 ml). The solid obtained was filtered off and recrystallized from a mixture of ethanol:chloroform (3:1). The compound was identified as **4a** by spectroscopic and elemental analyzes. Yield = 230 mg (64%). The filtrate was evaporated to dryness and the bisindolylmethane **5a** isolated from the residue by column chromatography on silica gel column (eluent:hexane) and characterized.