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A simple and eco-friendly method for the aminomethylation of 3-substituted oxindoles via three-component Mannich reaction in aqueous media

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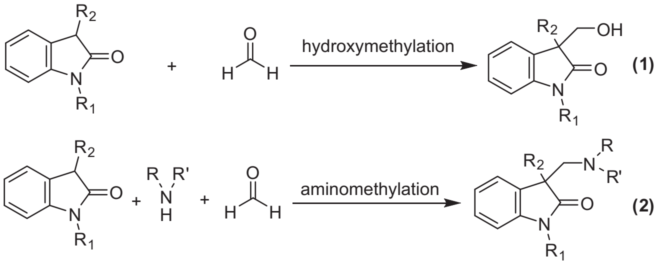
ABSTRACT

A simple and eco-friendly method for the aminomethylation of various 3-substituted oxindoles via three-component Mannich reaction in aqueous media has been established. A variety of oxindoles containing a quaternary carbon center, which comprises an aminomethyl group were obtained smoothly in good yields (up to 93%) with this method. Particularly valuable features, such as employing cheap and readily available formalin as a useful aminomethylation C1 unit and using water as a reaction medium, are embodied in this method.

Oxindoles bearing a quaternary carbon center at the C3 position are ubiquitous in nature and utilized as building blocks for alkaloid synthesis[1a,b] as well as development of potential therapeutic agents.[1c] In particular, oxindoles containing a hydroxymethyl or aminomethyl group at the C3 position are very attractive and valuable synthetic targets. Due to the ease of transforming hydroxymethyl and aminomethyl group to other functionalities, hydroxymethylation or aminomethylation oxindoles can act as potential intermediates for further elaboration. Actually, the addition reaction of prochiral 3-substituted oxindoles to formaldehyde or formaldehyde-derived imines provides a beneficial route to access oxindole derivatives containing a quaternary carbon center, which comprises a hydroxymethyl or aminomethyl group (Scheme 1). Although many transformations using 3-substituted oxindoles as nucleophiles (donor) reacting with various electrophiles (acceptor) have been developed,[2–4] to the best of our knowledge, the examples that can directly deliver oxindoles bearing a hydroxymethyl or aminomethyl group at the C3 position with formaldehyde or formaldehyde-derived imines as electrophiles are still scarce. Very recently, we developed one method for the hydroxymethylation of 3-substituted oxindoles with paraformaldehyde as C1 source and chiral bifunctional thiourea-tertiary amine as catalysts.[4b] Inspired by the success of hydroxymethylation of 3-substituted oxindoles,[4b] we hope to continue pursuing aminomethylation approach to access a series of oxindoles bearing an aminomethyl group at the C3 position via Mannich reaction.[5]

The Mannich reaction,[6] in which an enol or enolate attacks an imine or an iminium ion, is a powerful tool for introducing aminoalkyl fragments into organic molecules. Because formaldehyde does not form stable imines, in an attempt to avoid this issue, we chose to examine the three-component reaction of 3-substituted oxindoles, amine, and formaldehyde (Scheme 1, (**2**)). We envisioned that the iminium ion, generated in situ from formaldehyde and amine, was attacked by the C3-position of oxindoles to form the corresponding aminomethylation products. On the other hand, organic reaction in water has recently attracted great interest in organic synthesis due to its cost, safety, and environmental concern.[7] Herein, as continuation of our studies on the synthesis of oxindole-derivatives,[4,8] we report the first three-component Mannich reaction of 3-substituted oxindoles, formalin, and various secondary amines in aqueous media for the aminomethylation of 3-substituted oxindoles, particularly with formaldehyde-derived iminium ion generated in situ as electrophile.



Scheme 1.

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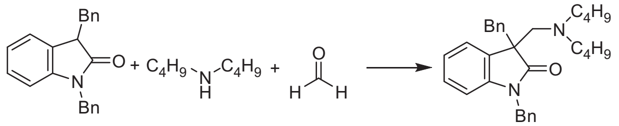
We initially investigated the three-component Mannich reaction of oxindole **1a** (0.3 mmol), dibutylamine (**2a**) (0.9 mmol), and paraformaldehyde (0.9 mmol) in various solvents (6.0 mL) at 35 °C (Table 1, entries 1–8). It was found that ethyl acetate (EtOAc) was superior to other examined solvents like chlorinated solvents, toluene, xylene, CH_3CN, and THF in view of the yield (Table 1, entry 4 vs entries 1–3 and 5–8). However, with further consideration on the development of environment-friendly chemistry, we tried to conduct Mannich reaction in water. To our delight, with further studies by adding sodium dodecyl sulfate (SDS) as additive or increasing reaction temperature, the desired product **4a** could be obtained smoothly in 85% yield in a shortened reaction time (3 h) (Table 1, entry 11). Afterward, the paraformaldehyde was replaced with more widely available formalin as C1 source for aminomethylation reaction,[9,10] we were pleased to find that **4a** could be obtained in 85% yield in 3 h (Table 1, entry 12). Finally, it was noted that a slightly higher yield of **4a** could be obtained with 2.0 equiv of **2a** and 4.0 equiv of formalin (based on the pure formaldehyde) at 90 °C (Table 1, entry 13).[9,10]

Next, the scope of the three-component Mannich reaction of various 3-substituted oxindoles with dibutylamine (**2a**) and formalin (**3**) was investigated (Table 2). Firstly, the 3-benzyl-oxindoles **1b** and **1c** were able to deliver the corresponding products **4b** in 88% yield and **4c** in 73% yield, respectively (Table 2, entries 1 and 2). Substrate **1d** could be converted to the desired aminomethylation product in 3 h,[11] but the aminomethylation product was decomposed to the starting material **1d** during the purification via flash chromatography (SiO_2) (Table 2, entry 3). We presumed that there was a retro-Mannich process occurring during the course of purification for this case. Afterward, *N*-benzyl-oxindoles **1e–g** were also investigated; we found that their corresponding aminomethylation products were able to be obtained in good

Table 1

The optimization studies on the aminomethylation of oxindole **1a**[a]



1a **2a** **3** **4a**

Entry	Solvent	**3**	*T* (°C)	Time (h)	Yield[b] (%)
1	$(ClCH_2)_2$	$(CH_2O)_n$	35	24	46
2	CH_2Cl_2	$(CH_2O)_n$	35	24	45
3	$CHCl_3$	$(CH_2O)_n$	35	24	36
4	EtOAc	$(CH_2O)_n$	35	24	90
5	Toluene	$(CH_2O)_n$	35	24	41
6	Xylene	$(CH_2O)_n$	35	24	23
7	CH_3CN	$(CH_2O)_n$	35	12	84
8	THF	$(CH_2O)_n$	35	24	38
9	Water	$(CH_2O)_n$	35	24	30
10	Water	$(CH_2O)_n$	35	24	43[c]
11	Water	$(CH_2O)_n$	70	3	85[c]
12	Water	Formalin	70	3	85[c]
13	Water	Formalin	90	3	87[c,d]

[a] Unless otherwise specified, the reactions were carried out in solvent 6.0 mL with 0.3 mmol **1a**, 3.0 equiv **2a** and 3.0 equiv **3** at the specified temperature.

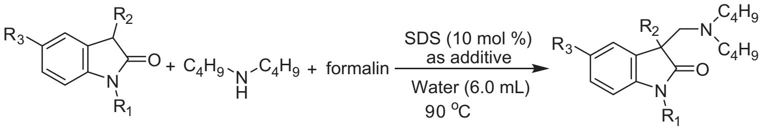
[b] Isolated yield after chromatographic purification.

[c] Using 10 mol % sodium dodecyl sulfate (SDS) as additive.

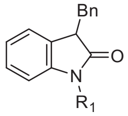
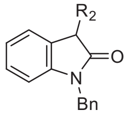
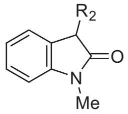
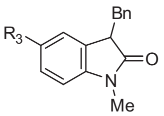
[d] The reaction was carried out in solvent 6.0 mL with 0.3 mmol **1a**, 2.0 equiv **2a** and 4.0 equiv formalin in the presence of 10 mol % SDS at 90 °C.

Table 2

Three-component reaction for the aminomethylation of various 3-substituted oxindoles[a,b]



1b-r **2a** **3** **4b-r**

Entry		**1**	Time (h)	**4**/Yield[c] (%)
1		R_1 = Me (**1b**)	3	**4b**/88
2		R_1 = MOM (**1c**)	5	**4c**/73
3		R_1 = Boc (**1d**)	3	**4d**/—[d]
4		R_2 = $CH(CH_3)_2$ (**1e**)	5	**4e**/81
5		R_2 = C_2H_5 (**1f**)	5	**4f**/80
6		R_2 = 4-$MeOC_4H_4$ (**1g**)	5	**4g**/82
7		R_2 = 4-$MeOPhCH_2$ (**1h**)	3	**4h**/86
8		R_2 = 4-$MePhCH_2$ (**1i**)	3	**4i**/82
9		R_2 = 3-$MePhCH_2$ (**1j**)	3	**4j**/90
10		R_2 = 4-$BrPhCH_2$ (**1k**)	3	**4k**/88
11		R_2 = 3-$BrPhCH_2$ (**1l**)	3	**4l**/78
12		R_2 = 4-$ClPhCH_2$ (**1m**)	3	**4m**/88
13		R_2 = 4-$MeOC_6H_4$ (**1n**)	5	**4n**/85
14		R_2 = 2-thienylmethyl (**1o**)	4	**4o**/75
15		R_2 = 1-naphthylmethyl (**1p**)	5	**4p**/72
16		R_3 = Me (**1q**)	3	**4q**/81
17		R_3 = Br (**1r**)	3	**4r**/93

[a] Unless otherwise specified, the reactions were carried out in 6.0 mL water with 0.3 mmol **1**, 2.0 equiv **2a** and 4.0 equiv formalin (based on the pure formaldehyde) in the presence of 10 mol % SDS at 90 °C.

[b] In these reactions, only trace amount hydroxymethylation product was observed.

[c] Isolated yield after chromatographic purification.

[d] The corresponding aminomethylation product **4d** was decomposed to the starting material **1d** during the purification via flash chromatography.

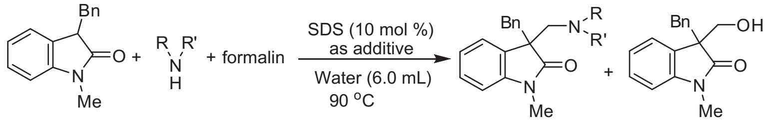
yields, regardless of alkyl or aryl group connected with the C3 position of oxindole scaffold (Table 2, entries 4–6). Subsequently, various 3-substituted *N*-methyl-oxindoles with different substitution patterns on the phenyl ring of benzyl group were also examined and good yields were obtained in these cases (Table 2, entries 7–12). Oxindole incorporating a 2-thienylmethyl group at the C3 position was also a viable substrate (Table 2, entry 14). Substrate bearing a bulky 1-naphtylmethyl group also gave smoothly its product in 72% yield (Table 2, entry 15). Using 3-aryloxindole **1n** as a substrate, the Mannich reaction also proceeded smoothly and afforded the product in 85% yield (Table 2, entry 13). In addition, *N*-methyl-3-benzyl-oxindoles bearing an electron-donating or electron-withdrawing group at the C5 position also could engage in the process efficiently (Table 2, entries 16 and 17).

Furthermore, the amine component of the three-component reaction was surveyed. Under the optimal reaction conditions, when dimethylamine (**2b**) was used as an amine partner, it was observed that the desired aminomethylation product **4s** was obtained in 56% yield, while the hydroxymethylation product **5** was also obtained in 38% yield (Table 3, entry 1). It is likely that there were three-component Mannich reaction and the aldol reaction of oxindole to formaldehyde proceeding simultaneously during the course and leading to their corresponding aminomethylation and hydroxymethylation products, respectively. However, when the amount of dimethylamine was increased up to 4.0 equiv from 2.0 equiv to oxindole, the same reaction gave **4s** in 74% yield and **5** in 20% yield (Table 3, entry 2). Subsequently, various other secondary amine **2c**–**j** were, respectively, employed for the reaction with **1b** and formalin (**3**) with substrates ratio 1:4:4 (**1b**/**2**/**3**) (Table 3, entries 3–10). We found that, except that **2e**, **2f**, and **2j** gave hydroxymethylation product **5** as the major product (Table 3, entries 5, 6 and 10), the other substrates mainly provided the desired aminomethylation products. In addition, when primary amine **2k** and **2l** were employed, only trace amount of aminomethylation products were found but hydroxymethylation product **5** could be obtained in poor yields (Table 3, entries 11 and 12).[12]

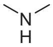
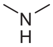
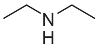
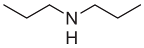
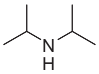
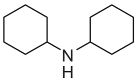
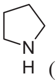
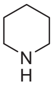
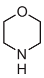
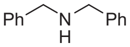
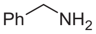
A postulated mechanism for the formation of aminomethylation and hydroxymethylation products is illustrated in Scheme 2. 3-Substituted oxindoles as nucleophiles attack the methylene iminium ion, generated by the condensation of secondary amines **2** and formaldehyde **3**, leading to the corresponding Mannich products **4**. On the other hand, possibly 3-substituted oxindoles attack formaldehyde component via aldol addition process, thereby yielding the hydroxymethylation product **5**. The Mannich reaction is

Table 3

Three-component reaction for the aminomethylation of 3-substituted oxindoles **1b** with various amines[a]



1b **2b-l** **3** **4s-x** **5**

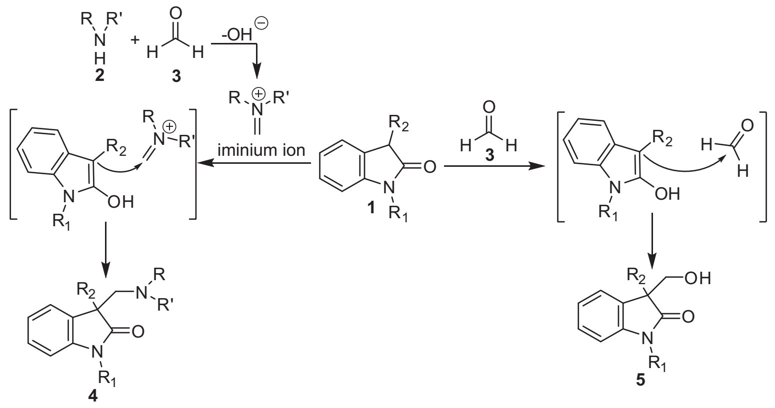
Entry	2	Time (h)	4/Yield[b] (%)	5/Yield[b] (%)
1[c,d]	 (**2b**)	3	**4s**/56	38
2	 (**2b**)	3	**4s**/74	20
3	 (**2c**)	3	**4t**/72	23
4	 (**2d**)	3	**4u**/75	18
5	 (**2e**)	5	Trace	64
6	 (**2f**)	5	Trace	68
7	 (**2g**)	3	**4v**/85	12
8	 (**2h**)	5	**4w**/87	11
9	 (**2i**)	5	**4x**/52	43
10	 (**2j**)	5	Trace	75
11	 (**2k**)	3	Trace	42
12	$Ph-NH_2$ (**2l**)	3	Trace	35

[a] Unless otherwise specified, the reactions were carried out in 6.0 mL water with 0.3 mmol **1b**, 4.0 equiv **2** and 4.0 equiv formalin (based on the pure formaldehyde) in the presence of 10 mol % SDS at 90 °C.

[b] Isolated yield after chromatographic purification.

[c] The solution of dimethylamine in water (40%) was used.

[d] The reaction was performed 6.0 mL water with 0.3 mmol **1b**, 2.0 equiv **2b** and 4.0 equiv formalin in the presence of 10 mol % SDS at 90 °C.



Scheme 2. Proposed reaction pathway for the aminomethylation of 3-substituted oxindoles.

presumably of great priority compared to the aldol reaction in the reaction system, therefore, the aminomethylation products were observed as major products in most cases. In contrast, in the case of using some bulky structure amines or primary amines as substrates (Table 3, entries 5 and 6 and 10–12), maybe the preferential reaction is aldol reaction, thus affording the hydroxymethylation product as the major product.

In conclusion, we have developed a simple and eco-friendly approach for the aminomethylation of various 3-substituted oxindoles with the three-component Mannich reaction of 3-substituted oxindoles, secondary amines, and formalin. This transformation can furnish a variety of oxindoles bearing a quaternary carbon center at the C3 position in good yields with 10% SDS as additive in water. Particularly valuable features of this method include employing cheap and easily available formalin as useful aminomethylation C1 unit, using water as a reaction medium. Meanwhile, we also observed hydroxymethylation product as a major product in some examples, while using bulky structure secondary amines or primary amines as substrates. Further studies toward the development of more efficient protocol for the preparation of structurally diverse oxindoles are ongoing in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.12.060.

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9. Formalin we used in this work, is an aqueous solution of formaldehyde and contains 37% formaldehyde by volume.
10. The amount of formalin used in the reaction is based on the pure formaldehyde.
11. The compound **4d** was confirmed by ^{1}H NMR spectroscopy of the crude reaction mixture and TLC analysis.
12. The trace amount of aminomethylation products (<10% yield) were monitored by TLC.