

Condensation of Indoles and Aldehydes in Subcritical Water without the Addition of Catalysts

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Abstract

A series of 3,3'-diindolylmethanes were prepared in high yields from indoles and aldehydes under subcritical water conditions without the addition of catalysts. 3-Alkenylindoles were also obtained in good yields from aldehydes bearing benzylic hydrogen atoms.

3,3'-Diindolylmethane (DIM) scaffolds, isolated from natural sources,¹ have been receiving increasing attention because of their medicinal properties, including anticancer activity.² A convenient approach for the synthesis of DIM and its derivatives is based on the reaction of indoles with aldehydes³ in the presence of Brønsted or Lewis acids,⁴ iodine,⁵ montmorillonite,⁶ zeolite,⁷ silica gel,⁸ nanoporous aluminosilicate,⁹ surfactants,¹⁰ TiO₂ nanoparticles,¹¹ benzyltriphenylphosphonium tribromide,¹² glycerol,¹³ and amino catalysts.¹⁴ Direct synthesis of DIM from benzyl alcohols and indoles has been recently reported.¹⁵ Solvent-free reactions of DIMs have also been reported.^{4f,16}

During our study on environmentally benign organic synthesis,¹⁷ we became interested in reactions in high-temperature water.^{18,19} Water that is super-heated above its boiling point shows unique characteristics that are not observed in the case of water at ambient temperature, i.e., a marked increase in the ionic product and a decrease in the dielectric constant.²⁰ Therefore, superheated water is a very good solvent for most organic compounds; acid/base reactions can proceed without the addition of catalysts and organic compounds become miscible. Aside from regeneration of useful resources from organic wastes in near-critical water,²¹ there have been few reports of organic synthesis in water at high temperatures. Herein, we report the direct coupling of indoles and aldehydes in subcritical water without any added catalyst.

Results and Discussion

We started our study with the reaction of indole **1a** and benzaldehyde (**2a**) as model partners according to the conditions used in the reactions between alcohols and indoles.¹⁷ A mixture of **1a** (1.2 mmol) and **2a** (1.0 mmol) in water (15 cm³) was placed in a Teflon container (30 cm³) supported by an SUS 316 outer jacket²² and heated in an electric dryer for 1 h at the set temperature.

At 100 °C, DIM **3a** was obtained in 39% yield, and both the starting materials remained largely intact (Entry 1). With an increase in temperature, the yield increased and reached a plateau at 150 °C (Entries 3 and 4). However, at 60 °C, the DIM **3a** was obtained only in 66% yield, even after the reaction was continued for 6 h (Entry 5). The maximum yield was observed when the reaction was carried out at 100 °C for 6 h (Entry 6). When a stoichiometric amount of **1a** (2 mmol) was used and the reaction was performed at 170 °C for 1 h, **3a** was obtained in 80% yield (Entry 7). In this screening, all reactions gave **3a** alone and excess benzaldehyde was partially recovered. Further cyclization²³ from **3a** with **2a** leading to indolo[3,2-*b*]carbazole (2:2 product) was not observed during these reactions.

The conditions shown in Table 1 presumably did not reflect the real temperature in the reaction vessel, because temperature was adjusted at the electric dryer, and there may have been a non-negligible delay before the final temperature was attained by the interior of the reactor. The results in Entries 1 and 6 indicated, however, that 6 h would be sufficient for completion of the reaction. Thus, we used $170 \,^{\circ}$ C and 6 h for subsequent reactions performed with a ratio of 2:1 **1a** to carbonyl compound and proceeded to determine the scope and limitations of carbonyl substrates. The results are shown in Table 2.

With benzaldehyde, **3a** was obtained in 90% yield. *p*-Anisaldehyde, *p*-hydroxybenzaldehyde, and *p*-formylbenzoic

Table 1. Reactions of indole 1a with benzaldehyde^{a)}

Ia H	+ PhCHO 2a		Ph 3a NH
Entry	1a:2a	Conditions	Yield/% ^{b)}
1	1.2:1	100 °C, 1 h	39
2	1.2:1	120 °C, 1 h	67
3	1.2:1	150 °C, 1 h	88
4	1.2:1	170 °C, 1 h	89
5	1.2:1	60 °C, 6 h	66
6	1.2:1	100 °C, 6 h	95
7	2:1	170 °C, 1 h	80

a) Conditions: all reactions were conducted using **1a** (1.2 mmol or 2.0 mmol) and **2a** (1.0 mmol) in water (15 cm³), in a Teflon container (30 cm³). b) Based on **1a**.





a) All reactions were performed with 1a (2.0 mmol) and aldehyde (1.0 mmol) in water (15 cm³).



Scheme 1. Reactions of 1-, 2-, and 3-methylindoles.



Scheme 2. Effect of acid, base, and water.

acid gave the corresponding DIMs **3b**, **3c**, and **3e** in high yields, although *p*-dimethylaminobenzaldehyde afforded **3d** in relatively low yield. The presence of electron-withdrawing groups such as ester, cyano, and nitro groups, at the *ortho* and *para* positions of benzaldehyde did not affect the reaction, and **3f**-**3h** were obtained in high yields. The cyano and ester groups remained intact under the subcritical conditions. However, the sterically demanding *o*-substitution resulted in a lower yield of **3i**. The heteroaromatic aldehyde 3-thiophenecarboxaldehyde proved to be a good substrate, while indolyl aldehyde proved to be a poor substrate and gave triindolylmethane **3k** in low yield. Aliphatic aldehydes were converted into the corresponding DIMs **3l**-**3n** in moderate yields.

We next turned our attention towards substituted indoles. 1-, 2-, and 3-Methylindoles were subjected to the reaction with **2a**. 1-Methylindole and 2-methylindole gave the corresponding DIMs **3o** and **3p**, respectively, in good yields whereas 3-methylindole gave 2,2'-DIM **3q** in only 48% yield (Scheme 1).

In order to examine the role of water, the reaction was carried out in both DMSO and *o*-xylene, as representative polar and nonpolar solvents. When the reaction of **1a** and **2a** was performed in *o*-xylene at 100 °C for 6 h, **3a** was obtained in 7% yield and 74% of **1a** were recovered. In DMSO only trace amounts of **3a** were obtained at 100 °C and even at 170 °C **3a** was generated in only 35% yield. These results clearly indicate that the reaction is promoted by water. Next, the effect of acid/base addition and water as a solvent was examined to obtain mechanistic insights into this reaction (Scheme 2). Addition of sulfuric acid (5 mol%) to the reaction with cyclohexane-carbaldehyde increased the yield of **3m** to 92%, while the



Scheme 4. Reaction of phenylacetaldehyde with indoles.

addition of sodium hydroxide (10 mol %) and the reaction under solvent-free conditions at 170 $^{\circ}\rm C$ resulted in lower yields.

In order to gain further information about the mechanism, a pair of aromatic aldehydes possessing electron-donating and electron-withdrawing groups was reacted competitively with **1a** (Scheme 3). The strong preference for more electrophilic **3g** can be explained by a Friedel–Crafts mechanism.

3-Alkenylindole derivatives are useful intermediates in the synthesis of natural products, exemplified by a dienophile for Diels–Alder cyclization²⁴ and a precursor to unsymmetrical DIMs.²⁵ We found that an aldehyde bearing benzylic hydrogen atoms gave the corresponding 3-alkenylindoles at higher reaction temperatures as reported.²⁶ When **1c** was treated with phenylacetaldehyde, a mixture of DIM **5a** and 3-styrylindole **6a** was obtained (Scheme 4). At 120 °C, **5a** was exclusively formed, while the formation of 3-alkenylindole **6a** become gradually predominant at higher temperatures. When 1,2-dimethylindole was subjected to the reaction, 3-alkenylindole **6b** was obtained even at 120 °C, and a selective formation of **6b** was achieved at 220 °C.

A plausible reaction mechanism for the alkylation and alkenylation is depicted in Scheme 5: indoles undergo acidcatalyzed alkylation with aldehydes at the 3-position to give iminium intermediates **A**, which react with a second indole to give the corresponding DIMs. In the case of phenylacetaldehyde, however, abstraction of the benzylic proton can provide an alternative path to 3-alkenylindoles by elimination of an indole moiety from DIM **5** and/or elimination of the benzylic proton directly from the iminium intermediate **A**. The above scenario leading to 3-alkenylindoles has already been proposed for reactions in the presence of Brønsted or Lewis acids.²⁶ To



Scheme 5. A plausible reaction mechanism.



Scheme 6. Elimination of 2-methylindole from DIM 5a.

confirm the elimination of an indole molecule from DIM under the present conditions, we exposed isolated DIM 5a alone to high temperatures. At 220 °C, 5a was completely converted into 3-alkenylindole 6a and 1c within 6h, with a ratio of 1:1 n good yields in the presence or absence of water, indicating that elimination of 2-methylindole from 5a occurred effectively at this temperature irrespective of the presence of water (Scheme 6). At 120 °C, 5a remained intact under both the conditions. A comparison of the results in Schemes 4 and 6 confirms that multiply substituted indoles tend toward formation of 3-alkenylindole 6 even at a lower temperatures while the elimination of mono-substituted indoles requires higher temperatures. In the case of unsubstituted indole, only the corresponding DIM was obtained in 67% yield at 170 °C, while at 220 °C a complex reaction mixture was obtained wherein neither the corresponding DIM nor 3-alkenylindole could be found. These observations can be accounted for by assuming that substitution of indole with alkyl groups increases the stability of the intermediate A by their electron-donating nature and facilitates the elimination of indole and proton.^{26c}

Finally, we assessed the present reaction with special emphasis on the *E*-factor.²⁷ The proposed protocol can obviate the need for extraction by an organic solvent because water alone is employed as the reagent/solvent, provided that the reaction goes to completion and the product is insoluble in water. A quick look at Table 2 shows that **3f**, obtained as a solid, was almost quantitatively obtained under the present conditions. Thus, we tried to isolate **3f** directly from the reaction mixture by simple filtration. After the reaction was carried out for 6 h, the product was filtered off from the aqueous phase and dried under reduced pressure giving **3f** in 95% yield. These results clearly demonstrate that this process is greener than the conventional procedures; the amount of materials required for the reaction and purification is minimized, implying that the *E*-factor value is close to zero.

Conclusion

A variety of 3,3'-DIM derivatives were synthesized by the reaction between indoles and aldehydes in water under uncatalyzed subcritical conditions. In cases of aldehydes having benzylic hydrogen atoms, 3-alkenylindoles were obtained in good yields. The reaction can be easily conducted by heating in an electric oven, a commonly available laboratory device. The reaction is safe and clean, since non-flammable water alone is used as the reagent/solvent. This work may expand the synthetic utility of high-temperature water in the field of organic chemistry. Further study of reactions under these conditions is now in progress.

Experimental

Materials and Methods. All reactions were carried out in ion-exchanged water ($<0.08 \text{ mS cm}^{-1}$), which was obtained by an ORGANO PURE LITE PRB-002A. Teflon containers and SUS 316 outer jackets were purchased from Shikokurika Co., Ltd.^{22a}

Representative Procedure for Preparation of 3a (Entry 7 in Table 1). A mixture of benzaldehyde (102μ L, 1.0 mmol), indole (234 mg, 2.0 mmol), and ion-exchanged water (15 mL) was introduced into a Teflon container with a volume filling factor of 50%. The Teflon container placed in an SUS 316 outer jacket was heated at 170 °C in an electric drier for 1 h. After the reactor was cooled to room temperature, the product was extracted with ether. The organic solution was washed with brine and concentrated under reduced pressure to give the crude product (310 mg), which was analyzed by ¹H NMR using 1,3,5trimethoxybenzene (51 mg, 0.30 mmol) as a standard material ($\delta = 6.09$, 3H). The yield of **3a** was determined to be 80% by integrating the ¹H NMR peak ($\delta = 5.89$, 1H).

General Procedure for Preparation of DIM in Table 2. A mixture of aldehyde (1.0 mmol), indole (2.0 mmol), and ionexchanged water (15 mL) was introduced into a Teflon container with a volume filling factor of 50%. The mixture was heated at 170 °C for 6 h, as above-mentioned. After the reactor was cooled to room temperature, the product was extracted with ether. The organic solution was washed with brine and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (hexane/EtOAc 5:1 gradually to EtOAc) to afford the corresponding diindolylmethane.

Preparation of 3f without Extraction. A mixture of methyl 4-formylbenzoate (164 mg, 1.0 mmol), indole (234 mg, 2.0 mmol), and ion-exchanged water (15 mL) was introduced into a Teflon container with a volume filling factor of 50%. The mixture was heated at $170 \,^{\circ}$ C for 6 h, as above-mentioned. After the reactor was cooled to room temperature, the product

was filtered off and dried under reduced pressure yielding 3f (363 mg) in 95% yield. ¹H NMR analysis confirmed the purity of the product.

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Supporting Information

Experimental procedures and characterization of products, and copies of ¹H and ¹³C NMR spectra. This material is available electronically on J-STAGE.

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