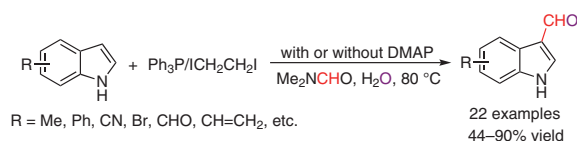


# Triphenylphosphine/1,2-Diiodoethane-Promoted Formylation of Indoles with *N,N*-Dimethylformamide

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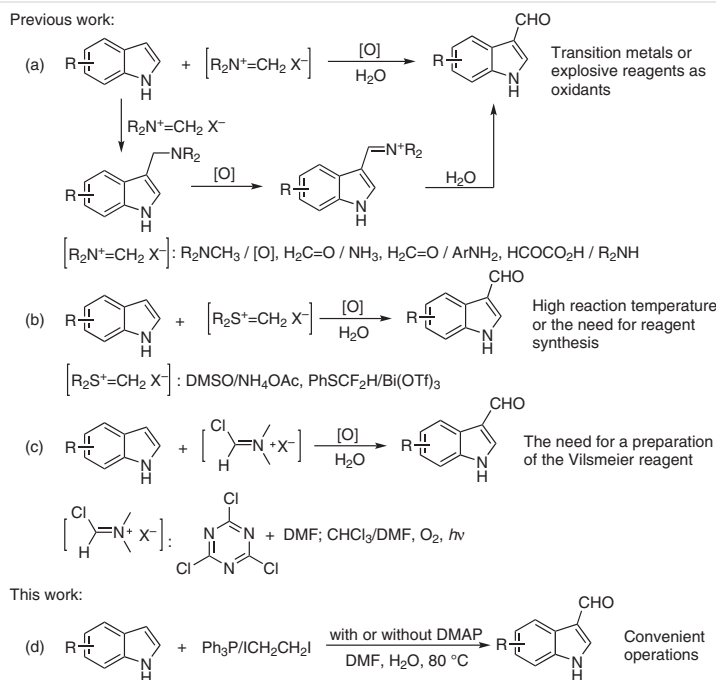
**Abstract** Despite intensive studies on the synthesis of 3-formylindoles, it is still highly desirable to develop efficient methods for the formylation of indoles, due to the shortcomings of the reported methods, such as inconvenient operations and/or harsh reaction conditions. Here, we describe a Ph<sub>3</sub>P/ICH<sub>2</sub>CH<sub>2</sub>I-promoted formylation of indoles with DMF under mild conditions. A Vilsmeier-type intermediate is readily formed from DMF promoted by the Ph<sub>3</sub>P/ICH<sub>2</sub>CH<sub>2</sub>I system. A one-step formylation process can be applied to various electron-rich indoles, but a hydrolysis needs to be carried out as a second step in the case of electron-deficient indoles. Convenient operations make this protocol attractive.

**Key words** formylation, indoles, aldehydes, Vilsmeier-type intermediate, dimethylformamide

The aldehyde (CHO) moiety is commonly found in various pharmaceuticals (e.g., voxelotor and alcaftadine), natural products (e.g., cinnamaldehyde and vanillin), and synthetic intermediates. Due to its high reactivity, the aldehyde group can be easily transformed into various functionalities, such as a hydroxy or carboxylic acid group. Therefore, great effort has been devoted toward the development of efficient methods for the installation of an aldehyde group. Formylation is an attractive and straightforward strategy, and a large number of formylation approaches have been developed, including the Vilsmeier–Haack reaction,<sup>1</sup> the Reimer–Tiemann reaction,<sup>2</sup> the Duff reaction,<sup>3</sup> and the Rieche reaction.<sup>4</sup> All these named reactions are effective for incorporation of CHO groups, but they can suffer from the need for harsh reaction conditions (e.g., strong bases), the use of moisture-sensitive reagents (e.g., POCl<sub>3</sub>), or a narrow tolerance of functionality.

Because the indole moiety is a key motif in many biologically active molecules,<sup>5</sup> the incorporation of a formyl group at the 3-position of indoles has received much attention. A widely used formylation strategy involves a Mannich-type addition followed by an oxidation/hydrolysis (Scheme 1a).<sup>6</sup> In this strategy, a methylamine usually acts as the carbon source for the CHO group under oxidative conditions.<sup>6a–j</sup> The oxidation of the methylamine gives an iminium ion, and attack by the iminium ion on the indole provides a Mannich addition product; subsequent oxidation and hydrolysis deliver a 3-formylindole. Besides methylamines, other amine systems can also be effective in formylation, such as H<sub>2</sub>C=O/NH<sub>3</sub>, H<sub>2</sub>C=O/ArNH<sub>2</sub>, or HC(O)CO<sub>2</sub>H/R<sub>2</sub>NH.<sup>6k–m</sup> These amine systems can be converted into iminium ions under various conditions, permitting a subsequent formylation. Despite extensive studies, this strategy can suffer from the need to use transition metals or explosive reagents as oxidants. The thionium ion can also function as a carbon source for the CHO group, and this formylation approach features a wide substrate scope and broad functional-group tolerance (Scheme 1b).<sup>7</sup> However, a high reaction temperature (150 °C) and the need to synthesize the reagent (PhCF<sub>2</sub>H) can limit the range of applicability of this approach. The Vilsmeier–Haack reaction has also proved to be an efficient method for formylation,<sup>1</sup> and a new approach for the generation of Vilsmeier intermediate has been effectively applied in the synthesis of 3-formylindoles (Scheme 1c). However, the Vilsmeier reagent has to be prepared in advance. Consequently, a one-pot protocol for the formylation of indoles is desirable.

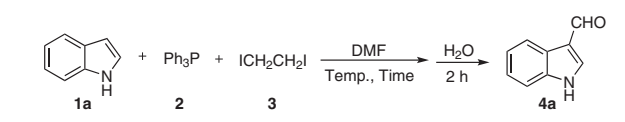
Previously, we have shown that trivalent phosphorus compounds (R<sub>3</sub>P) can react rapidly with 1,2-diiodoethane (ICH<sub>2</sub>CH<sub>2</sub>I) to generate an iodophosphonium species (R<sub>3</sub>P<sup>+</sup>I<sup>-</sup>) that can activate hydroxy and aldehyde groups, permitting deoxyfunctionalizations of alcohols and aldehydes.<sup>8</sup> If DMF is used as the reaction solvent, a Vilsmeier-type intermedi-



Scheme 1 Formylation of indoles

ate is readily generated.<sup>8b,c</sup> An  $R_3P/X_2$  ( $X = Br$  or  $I$ ) system in DMF can also generate a Vilsmeier-type intermediate, but requires the use of a toxic dihalogen molecule.<sup>9</sup> Herein, we report a Vilsmeier-derived formylation of indoles with the  $R_3P/ICH_2CH_2I$  system in DMF. The reactions proceeded smoothly under an air atmosphere to give the expected products in moderate to high yields (Scheme 1d). Convenient operations might make this protocol attractive.

Initially, we thought that the reaction of indole with the Vilsmeier-type intermediate generated in situ and the subsequent hydrolysis might need to be performed as a two-step process, and we therefore screened several two-step procedures (Table 1, entries 1–5). The expected product was indeed formed at 20 °C, albeit in only a 26% yield (entry 1). Elevating the reaction temperature significantly increased the yield (entries 2 and 3), and an 87% yield was obtained at 80 °C (entry 3). No increase in the yield was observed on further elevating the temperature (entry 4). The yield was not decreased by shortening the reaction time for the first step (entry 5). To our delight, however, combining the two steps into one step also gave a high yield (entry 6). Apparently, the absence of any water-sensitive reagent permits the one-step process to occur smoothly. A 90% yield was obtained on increasing the loadings of both  $Ph_3P$  and  $ICH_2CH_2I$  (entry 7), but the yield decreased on increasing the loading of either  $Ph_3P$  or  $ICH_2CH_2I$  alone (entries 8 and 9). The use of an excess of indole also led to a decrease in the yield (entry 10).

Table 1 Optimization of the Reaction Conditions<sup>a</sup>


Entry	<b>1a/2<sup>b</sup></b>	Temp (°C)	Time (h)	Yield <sup>c</sup> (%)
1	1:1:1	20	2	26
2	1:1:1	40	2	58
3	1:1:1	80	2	87
4	1:1:1	120	2	87
5	1:1:1	80	1	85
6	1:1:1	80	0	80
7	1:1.5:1.5	80	0	90
8	1:1:1.5	80	0	59
9	1:1.5:1	80	0	78
10 <sup>d</sup>	1.5:1:1	80	0	77

<sup>a</sup> Reaction conditions: **1a** (0.2 mmol), **2**, **3**, DMF (1 mL), stirring for the indicated time; then  $H_2O$  (3 mL), stirring, 2 h.

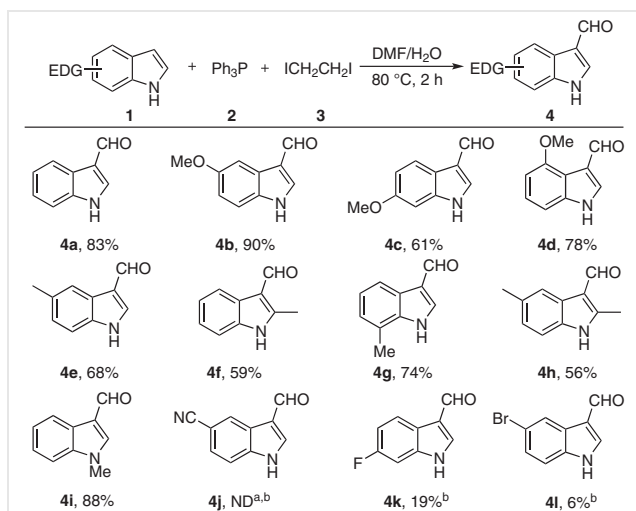
<sup>b</sup> Molar ratio.

<sup>c</sup> Determined by  $^1H$  NMR with 1,3,5-trimethoxybenzene as an internal standard.

<sup>d</sup> Indole (0.3 mmol) was used.

With the optimal reaction conditions in hand (Table 1, entry 7), we investigated the substrate scope of the  $Ph_3P/ICH_2CH_2I$ -promoted formylation of indoles with DMF. As shown in Scheme 2, it was not necessary to protect the

N–H group, and the one-step process could be extended to various electron-rich indoles. The reactions proceeded smoothly to give the desired products in moderate to high yields. However, no product was detected in the case of indoles containing strongly electron-withdrawing groups (**4j**), and low yields were obtained if weakly electron-withdrawing groups were attached (**4k** and **4l**).



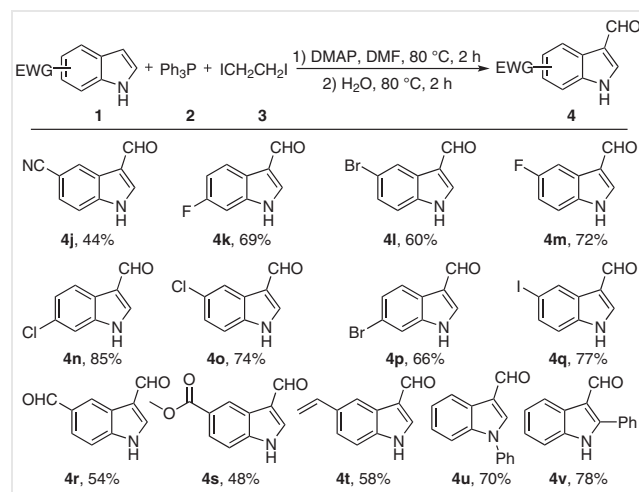
**Scheme 2** Formylation of electron-rich and electron-neutral indoles. Reagents and conditions: **1** (0.5 mmol),  $\text{Ph}_3\text{P}$  (0.75 mmol),  $\text{ICH}_2\text{CH}_2\text{I}$  (0.75 mmol) in  $\text{DMF-H}_2\text{O}$  (2 mL + 5 mL), 80 °C, 2 h. <sup>a</sup> ND = not detected. <sup>b</sup> Determined by  $^1\text{H}$  NMR spectroscopy.

The successful formylation of electron-rich indoles encourages us to further screen conditions for the reactions of electron-deficient indoles.<sup>10</sup> To our delight, the reaction proceeded smoothly on carrying out the reaction as a two-step process; moreover, the addition of 4-(*N,N*-dimethylamino)pyridine (DMAP) increased the yield of **4l** by a further 18%, as determined by  $^1\text{H}$  NMR analysis (for details of the screening of the reaction conditions, see the Supporting Information). As shown in Scheme 3, all the desired products were obtained in moderate yields. Various functional groups were tolerated, including nitrile, aldehyde, ester, and alkene groups. Although a two-step procedure is required, the protocol features convenient operations and uses readily available reagents.

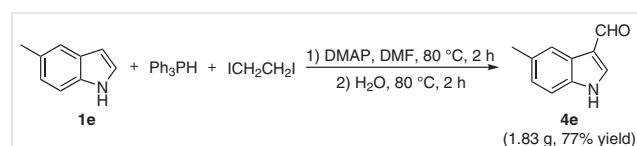
To further demonstrate the synthetic utility of this transformation, a gram-scale reaction was performed. For the electron-rich indole **1e**, a two-step process gave the desired product **4e** in 77% yield (Scheme 4), indicating that the DMAP process can be applied to both electron-rich and electron-deficient indoles.

Partly based on our previous studies,<sup>8</sup> we propose the reaction mechanism shown in Scheme 5.  $\text{Ph}_3\text{P}$  reacts rapidly with  $\text{ICH}_2\text{CH}_2\text{I}$  to give either  $\text{Ph}_3\text{P}(\text{I})_2$  (**A**) or  $\text{Ph}_3\text{P}^+\text{I}^-$  (**B**), which are in equilibrium with each other.  $\text{Ph}_3\text{P}^+\text{I}^-$  (**B**) is highly reactive toward O-nucleophiles and is therefore readily attacked by DMF to generate intermediate **C**. The re-

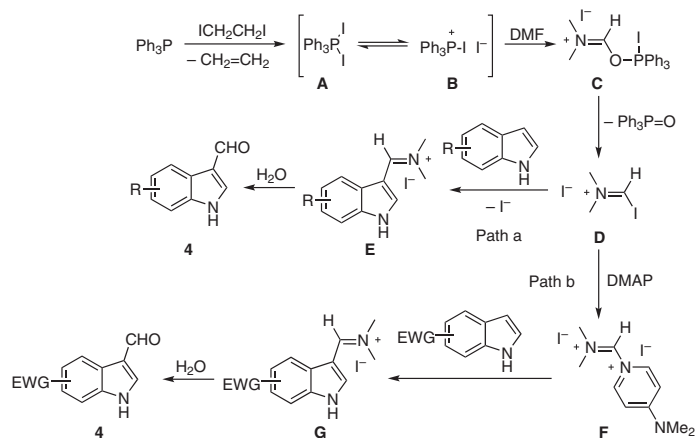
lease of stable  $\text{Ph}_3\text{P}=\text{O}$  is a driving force for the conversion of intermediate **C** into the Vilsmeier-type intermediate **D**. Attack by the electron-rich indole on intermediate **D** and subsequent hydrolysis provides the final product (Path a). If the indole is not sufficiently nucleophilic, intermediate **D** can be readily hydrolyzed by water instead of being attacked by indoles in the one-step formylation. Electron-deficient indoles show a lower nucleophilicity and therefore cannot undergo formylation by the one-step process. The two-step process occurs smoothly, because intermediate **D** is not easily hydrolyzed in the absence of water. Regarding the role of DMAP in the formylation of electron-deficient indoles, the desired product can still be obtained in a moderate yield in its absence (see Supporting Information), indicating that DMAP is not a crucial reagent. Although it has been reported that  $\text{Ph}_3\text{P}(\text{I})_2$  (**A**) can react directly with an organic base,<sup>11</sup> we still believe DMAP activates intermediate **D**. Our previous studies have shown that  $\text{Ph}_3\text{P}$  is completely and immediately consumed upon mixing with  $\text{ICH}_2\text{CH}_2\text{I}$  in DMF.<sup>8b,c</sup> Because  $\text{Ph}_3\text{P}^+\text{I}^-$  (**B**) is quite reactive toward DMF, and DMF is used in a large excess,  $\text{Ph}_3\text{P}^+\text{I}^-$  (**B**) is more likely to react with DMF than with DMAP. DMAP might react with intermediate **D** to produce a more-electrophilic species **F**, which might be attacked by electron-deficient indoles to generate intermediate **G** (Path b). Electron-deficient indoles might be transformed by both Path a and Path b to afford the final products.



**Scheme 3** Formylation of electron-deficient indoles. Reagents and conditions: **1** (0.5 mmol),  $\text{Ph}_3\text{P}$  (0.75 mmol),  $\text{ICH}_2\text{CH}_2\text{I}$  (0.75 mmol), DMAP (0.5 mmol), DMF (2 mL), 80 °C, 2 h, then  $\text{H}_2\text{O}$  (5 mL), stirring, 80 °C, 2 h.



**Scheme 4** A gram-scale reaction



**Scheme 5** A plausible reaction mechanism

In summary, we have developed a  $\text{Ph}_3\text{P}/\text{ICH}_2\text{CH}_2\text{I}$ -promoted formylation of indoles with DMF under mild conditions. The one-step process can be extended to various electron-rich indoles. In the case of electron-deficient indoles, although a hydrolysis needs to be carried out as a second step, the overall series of operations is still quite convenient. The ready availability of reagents and the convenient operations make this protocol attractive.

## Conflict of Interest

The authors declare no conflict of interest.

## Funding Information

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-1675-1043>.

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- (10) (a) **Formylation of Electron-Rich Indoles; General Procedure** A 25 mL tube was charged with  $\text{Ph}_3\text{P}$  (0.75 mmol, 1.5 equiv),  $\text{ICH}_2\text{CH}_2\text{I}$  (0.75 mmol, 1.5 equiv), the appropriate indole **1** (0.5 mmol, 1 equiv), DMF (2 mL), and  $\text{H}_2\text{O}$  (5 mL) under air, and the mixture was stirred at 80 °C for 2 h. The mixture was then cooled to rt and sat. aq brine was added. The crude organic product was extracted with  $\text{CH}_2\text{Cl}_2$ , and the combined organic

phase was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (silica gel, pentane–EtOAc).

**Formylation of Electron-Deficient Indoles; General Procedure**

A 25 mL tube was charged with  $\text{Ph}_3\text{P}$  (0.75 mmol, 1.5 equiv),  $\text{ICH}_2\text{CH}_2\text{I}$  (0.75 mmol, 1.5 equiv), the appropriate indole **1** (0.5 mmol, 1 equiv), DMAP (0.5 mmol, 1 equiv), and DMF (2 mL) under air, and the mixture was stirred at 80 °C for 2 h.  $\text{H}_2\text{O}$  (5 mL) was added and the mixture was stirred at 80 °C for a further 2 h. Similar workup to the above gave the pure product.

**5-Vinyl-1H-indole-3-carbaldehyde (4t)**

White solid; yield: 49.4 mg (58%); mp 164.9–166.7 °C. IR (neat): 3148, 1635, 1615, 1522, 1473, 1440, 1392, 1245, 1129, 911, 819, 790  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 12.18 (s, 1 H),

9.94 (s, 1 H), 8.28 (s, 1 H), 8.14 (s, 1 H), 7.52–7.41 (m, 2 H), 6.85 (dd,  $J$  = 17.5, 10.9 Hz, 1 H), 5.76 (d,  $J$  = 17.6 Hz, 1 H), 5.18 (d,  $J$  = 10.9 Hz, 1 H).  $^{13}\text{C}$  NMR (400 MHz,  $\text{DMSO}-d_6$ ):  $\delta$  = 185.50 (s), 139.36 (s), 137.94 (s), 137.35 (s), 132.08 (s), 124.88 (s), 122.02 (s), 119.57 (s), 118.80 (s), 113.06 (s), 112.75 (s). HRMS (EI):  $m/z$   $[\text{M}]^+$  calcd for  $\text{C}_{11}\text{H}_9\text{NO}$ : 171.0684; found: 171.0682. (b) Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J.-N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006. (c) Dorta, R. L.; Rodríguez, M. S.; Salazar, J. A.; Suárez, E. *Tetrahedron Lett.* **1997**, *38*, 4675.

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