A Novel Protocol for Construction of Indolylmethyl Group at Aldehydes or Ketones

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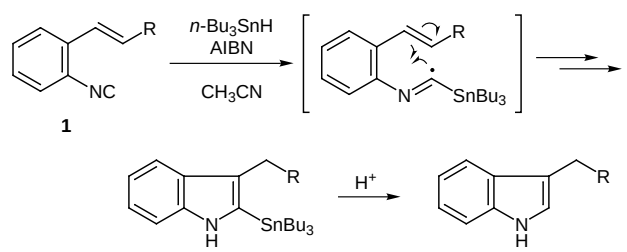
Abstract: A new method for introduction of indolylmethyl group to aldehydes or ketones using diethyl (*o*-isocyanophenylmethyl)phosphonate through Horner-Wadsworth-Emmons condensation, thiol-mediated radical cyclization, and the subsequent desulfurization is described. The Horner-Wadsworth-Emmons reagent was prepared from 2-nitrobenzaldehyde in a concise three-step sequence.

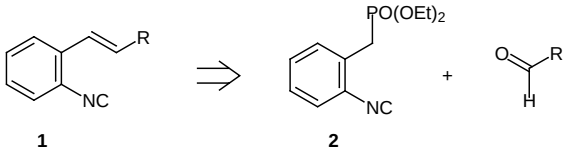
Key words: 3-substituted indoles, diethyl (*o*-isocyanophenylmethyl)phosphonate, Horner-Wadsworth-Emmons condensation, 2-alkenylphenyl isocyanides, thiol-mediated radical cyclization

The indole nucleus is ubiquitous among a wide range of natural products, and the synthesis of this important structure have attracted attention of synthetic chemists.[2] Among the numerous methods that have been developed for the synthesis of indoles, there appear to be few practical and mild procedures available for the synthesis of 3-substituted indoles.[3] Although several methods for introduction of substituents at C3-position, namely nucleophilic addition to indoleines generated by gramine fragmentation[4] or Pd-catalyzed coupling with 3-haloindoles[5], have been well documented, these procedures have some problems with the versatility of the substituents and/or the stability of the substrates. Furthermore, the venerable Fischer indole synthesis using aldehydes often requires heating in the presence of strong acid, precluding therefore preparation of indoles with acid-labile functionalities. [6]

In our earlier studies, we reported a construction of substituted indoles by radical cyclization of 2-alkenylphenyl isocyanide **1** under mild and neutral conditions (Scheme 1).[7] The success of this methodology encouraged us to develop a suitable Horner-Wadsworth-Emmons reagents such as **2** (Scheme 2). This reagent would be condensed with a variety of aldehydes, which would provide a convenient access to a wide variety of 2-alkenylphenyl isocyanide **1**. Herein, we report a novel strategy for introduction of indole moiety using diethyl (*o*-isocyanophenylmethyl)phosphonate as an indolylmethylation reagent.

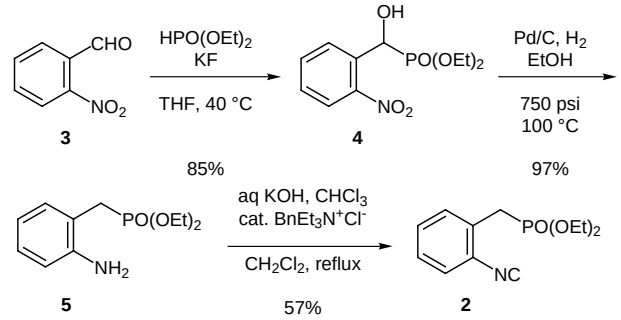


Scheme 1



Scheme 2

A facile route to the requisite Horner-Wadsworth-Emmons reagent using Pudovik reaction was established (Scheme 3).[8] 2-Nitrobenzaldehyde (**3**) was condensed with diethyl phosphite, followed by simultaneous catalytic hydrogenation of the nitro group and the hydroxy group at the benzylic position to give the corresponding aniline **5**. According to the Ugi's protocol, [9] **5** was converted to the desired isonitrile, diethyl (*o*-isocyanophenylmethyl)phosphonate (**2**) (47% overall yield from **3**). Because of the simple operations of the sequence, this protocol can be easily applied to a large-scale preparation.[10]

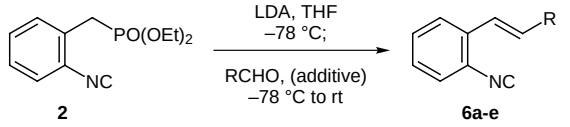


Scheme 3

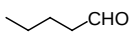
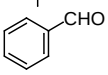
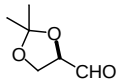
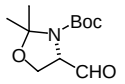
The new Horner-Wadsworth-Emmons reagent **2** has proven to be quite useful for the synthesis of a wide range of 2-alkenylphenyl isocyanides. A typical procedure involves addition of either aliphatic or aromatic aldehyde to an anion of **2**, generated by treatment with LDA at –78 °C, and raising the reaction temperature to 23 °C (Table 1, entries 1-3).[11] In contrast, glyceraldehyde[12] ace-

tonide and the Garner's aldehyde[13] were relatively less reactive, and as a result, an intramolecular attack of the benzylic anion of **2** to the isonitrile occurred to give diethyl 3-indolylphosphonate as a side product. This undesired side reaction could practically be suppressed by the addition of HMPA (entries 4 vs. 5).

Table 1 Horner-Wadsworth-Emmons Condensations with **2**

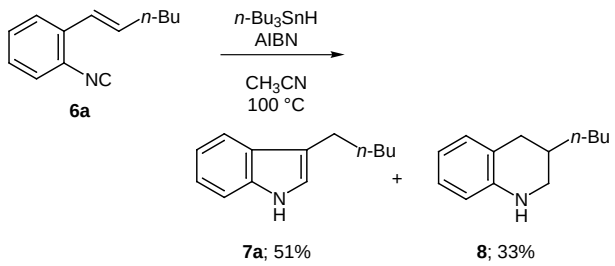


2 **6a-e**

Entry	RCHO	Additive	Yield (%)[a]	
1		—	87	**6a**
2		—	93	**6b**
3		—	90	**6c**
4		—	41[b]	**6d**
5		HMPA (5 eq)	80[c]	
6		HMPA (5 eq)	78	**6e**

a) Only *E* isomer was obtained unless otherwise noted.
b) *E*/*Z* ratio was 11 / 1. c) *E*/*Z* was 3.7/1.

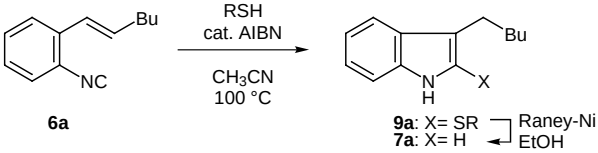
Depending on the substituents at the olefin terminus of the indole precursor **1**, there remains a problem in the radical-induced indole formation. While substrates with radical-stabilizing substituents generally provide cleanly the desired indoles, isonitriles bearing simple alkyl groups such as **6a** resulted in the formation of a considerable amount of tetrahydroquinoline **8** due to a 6-*endo*-*trig* radical cyclization (Scheme 4).[7a] In order to achieve selective 5-*exo*-*trig* cyclization, we have carefully reinvestigated the reaction conditions.



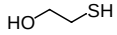
Scheme 4

Instead of the standard radical conditions using tri-*n*-butyltin hydride, we examined the conditions with a various thiols, and eventually found that the use of excess ethanethiol was quite effective for the radical cyclization (Table 2).[14] While only 31% of the desired indole **9a** was obtained using 1.5 equivalent of ethanethiol and AIBN in acetonitrile at 100 °C for 15 minutes, the use of five equivalents of ethanethiol improved the yield to 71% (entries 1 and 2). Under these reaction conditions, formation of the corresponding tetrahydroquinoline was not observed. Although the use of other thiols such as thiophenol or 2-mercaptoethanol also furnished the corresponding 2-indolyl sulfide in high yields, we chose ethanethiol because of the higher yields in the subsequent desulfurization process (entries 2 vs. 3 or 4). Finally, it was found that carrying out the cyclization and the desulfurization processes without isolation of 2-thioindoles **9** gave 3-substituted indoles **7** in higher yields.[15]

Table 2 Thiol-Mediated Radical Cyclization



6a

Entry	RSH	Equiv.	Yield (%)		
			6a to **9a**	**9a** to **7a**	**6a** to **7a**
1	EtSH	1.5	31	94	29
2	EtSH	5.0	71	94	67
3	PhSH	5.0	50	79	40
4		5.0	79	76	60
5	EtSH	5.0	—	—	83[a]

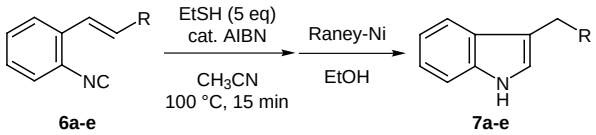
a) Compound **9a** was desulfurized immediately after removal of solvent due to its instability in air.

As summarized in Table 3, a range of 2-alkenylphenyl isocyanides were converted to the corresponding 3-substituted indoles by the optimized reaction conditions (vide supra).[16] In particular, this sequence is compatible with such acid-labile functionality as acetonide and Boc group (entries 4 and 5).

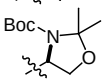
A further synthetic application of the present protocol is demonstrated by the reaction with ketones. Horner-Wadsworth-Emmons reaction of **2** with cyclohexanone took place smoothly in the presence of five equivalents of HMPA to give olefin **10** in 73% yield. Indole formation reaction and the subsequent desulfurization afforded 3-indolylcyclohexane **11** in almost quantitative yield (Scheme 5).

In conclusion, we have demonstrated a facile and versatile method for introduction of indolylmethyl group using a new Horner-Wadsworth-Emmons reagent. The facile and practical preparation of the indolylmethylation reagent coupled with mild cyclization conditions would make this protocol a general method for the construction of indolylmethyl unit from the structurally complex carbonyl compounds.

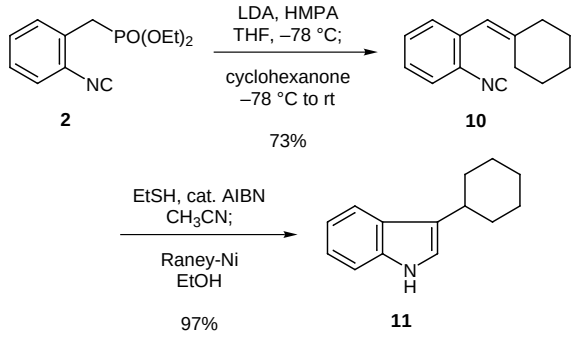
Table 3 Synthesis of 3-Substituted Indoles



6a-e **7a-e**

Entry[a]	R		Yield (%)
1		**6a**	83
2		**6b**	70
3		**6c**	76
4[b]		**6d**	61
5		**6e**	64

a) *E*-isomers of the starting olefins were used.
b) *E*/Z mixture (3.7/1) of the **6d** was used.



2 **10** **11**

Scheme 5

Acknowledgement

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(9) Weber, W. P.; Gokel, G. W.; Ugi, I. K. *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 530.
(10) **Preparation of 2**. To a solution of 2-nitrobenzaldehyde (**3**) (25.0 g, 0.165 mol) and diethyl phosphite (21.0 mL, 0.163 mol) in THF (300 mL) was added KF (56.0 g, 0.963 mol). After stirring at 40 °C for 2 h, the mixture was filtered, and the filtrate was evaporated in vacuo to give a crude mixture. Recrystallization (CH_2Cl_2-hexane) afforded phosphonate **4** as colorless crystals (39.5 g, 84%); Mp: 123.5 - 125.4 °C; IR (film, cm^{-1}) 3243, 2983, 2937, 2912, 2866, 1609, 1577, 1531, 1442, 1394, 1352, 1266, 1234, 1206, 1089, 1040, 970, 844, 786, 741, 710; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 4.03-4.18 (m, 4H), 5.91 (br s, 1H), 6.31 (d, *J* = 13.9 Hz, 1H), 7.43-7.47 (m, 1H), 7.68 (t, *J* = 7.6 Hz, 1H), 7.98-8.04 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1 (d, *J*(CP) = 24 Hz), 16.2 (d, *J*(CP) = 21 Hz), 63.3 (d, *J*(CP) = 27 Hz), 64.1 (d, *J*(CP) = 30 Hz), 65.5 (d, *J*(CP) = 638 Hz), 124.6, 128.3, 128.9, 133.0, 133.3, 147.5. Anal. Calcd for $C_{11}H_{16}NO_6P$: C, 45.68; H, 5.58; N, 4.84. Found: C, 45.64; H, 5.52; N, 4.74.
A solution of **4** (2.00 g, 6.91 mmol) in ethanol (70 mL) was hydrogenated over 10% Pd/C (0.40 g) at a hydrogen pressure of 750 psi at 100 °C for 3 days. Upon completion, the reaction mixture was filtered through a pad of Celite, and the filter cake was washed with EtOAc. The filtrate and washings were combined, and evaporated under reduced pressure to yield aniline **5** (1.63 g, 97%) as a yellow oil. The crude product was used for the next transformation without purification; IR (film, cm^{-1}) 3422, 3356, 3250, 2991, 2911, 1643, 1609, 1576, 1497, 1450, 1390, 1218, 1164, 1058, 1025, 959, 753; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.0 Hz, 6H), 3.10 (d, *J* = 20.8 Hz, 1H), 3.91-4.00 (m, 4H), 4.24 (s, 2H), 6.67-6.74 (m, 2H), 6.99-7.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2, 16.3, 29.3, 31.5, 62.2, 62.3, 117.0, 117.0, 117.1, 117.1, 118.9, 118.9, 128.0, 128.1, 131.4, 131.5, 145.8, 145.9.
To a solution of **5** (5.00 g, 20.6 mmol) in CH_2Cl_2 (40 mL) were added $CHCl_3$ (4.13 mL, 51.5 mmol), $BnEt_3NCl$ (94 mg, 0.41 mmol), and 50% aq KOH (40 mL). After a short induction period, the reaction mixture was stirred at reflux. Upon the completion, it was quenched by addition of water. The mixture was partitioned between ether and sat NH_4Cl. The aqueous layer was thoroughly extracted with ether. The extracts were combined and washed with brine, dried over K_2CO_3 and evaporated under reduced pressure. The residue was then purified by flash column chromatography on silica gel (MeOH-$CHCl_3$, 1:50) to yield isonitrile **2** (2.99 g, 57%); IR (film, cm^{-1}) 3481, 2991, 2938, 2917, 2121, 1642, 1484, 1450, 1416, 1383, 1257, 1197, 1164, 1051, 1025, 965, 858, 832, 766; ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 6H), 3.33 (d, *J* = 22.2 Hz, 2H), 4.06 (q, *J* = 7.0 Hz, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 7.25-7.52 (m, 4H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 16.0, 16.1, 28.6, 30.8, 62.0, 62.2, 126.1, 126.2, 126.2, 126.3, 126.8, 126.8, 126.8, 127.7, 127.7, 128.8, 128.9, 129.1, 129.1, 129.2, 129.2, 130.9, 131.0, 166.6. Anal. Calcd for $C_{12}H_{16}NO_3P$: C, 56.92; H, 6.37; N, 5.53. Found: C, 56.84; H, 6.47; N, 5.23.
(11) **General Procedure.** To a stirred solution of LDA in THF (prepared from 5.65 mmol of diisopropylamine and 5 mmol of *n*-BuLi in hexane) was added Horner-Emmons Reagent **2** (1.10 g, 4.35 mmol) at −78 °C. The mixture was stirred at −78 °C for 30 minutes before addition of aldehydes (3.92 mmol). The resulting mixture was stirred for additional 20

minutes at −78 °C and then allowed to warm to room temperature and stirred for another 1 hour before it was quenched by addition of 3 mL of water. The biphasic mixture was stirred at room temperature for 10 minutes and partitioned between ethyl ether and sat NH_4Cl. The aqueous layer was thoroughly extracted with ethyl ether. The extracts were combined and washed with brine, dried over Na_2SO_4 and evaporated on a rotary evaporator. Generally the residue was then purified by flash silica gel chromatography eluting with 5-25% ether in hexane.

Isocyanide 6b. IR (film, cm^{-1}) 3384, 2959, 2867, 2118, 1646, 1476, 1455, 1364, 1265, 1090, 1040, 972, 756; ^1H NMR (250 MHz, $CDCl_3$) δ 1.57 (s, 9H), 6.35 (d, *J* = 16.0 Hz), 6.62 (d, *J* = 16.0 Hz, 1H), 7.22 (dd, *J* = 1.2, 7.4 Hz) 7.29-7.32 (m, 2H) 7.55 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 29.2, 33.8, 119.0, 124.4, 125.6, 126.9, 127.2, 129.1, 134.4, 146.3, 166.3; HR-MS (EI) m/z calcd for $C_{13}H_{15}N$ 185.1204, found 185.1203.

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(15) We have found that 2-thioethylindole **9** was unstable in air. See, also; Nakagawa, M.; Yamaguchi, H.; Hino, T. *Tetrahedron Lett.* **1970**, *47*, 4035.

(16) **General Procedure**. A mixture of isonitrile (1.0 equiv.), ethanethiol (5.0 equiv.) and AIBN (0.1 equiv.) in dry acetonitrile in a sealed tube was heated at 100 °C for 15 minutes under an argon atmosphere. Upon cooling to room temperature, the solution was evaporated under reduced pressure. After removal of solvent, the residue was dissolved in ethanol, to which was added Raney-Ni, and then stirred at room temperature. The reaction mixture was then filtrated through a pad of Celite. The filtrate was evaporated under reduced pressure to yield 3-substituted indoles as analytically pure material.

7a; IR (film, cm^{-1}) 3316, 3054, 2962, 2850, 1618, 1460, 1423, 1343, 1234, 1101, 1010, 743; ^1H NMR (250 MHz, $CDCl_3$) δ 0.92 (t, *J* = 6.6 Hz, 3H), 1.14 (m, 4H), 1.74 (sep, *J* = 7.4 Hz, 1H), 2.77 (t, *J* = 7.4 Hz, 2H), 6.97 (s, 1H), 7.12 (t, *J* = 7.1 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.63 (d, *J* = 7.1 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 14.1, 22.6, 29.8, 30.7, 31.8, 111.0, 117.2, 119.0, 120.9, 121.8, 127.6, 132.2. HR-MS (EI) m/z calcd for $C_{13}H_{17}N$: 187.1361. Found: 187.1363.

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