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Synthesis of α^1-oxindole-α-hydroxyphosphonates under catalyst-free conditions using polyethylene glycol (PEG-400) as an efficient and recyclable reaction medium

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ABSTRACT

A simple, efficient, eco-friendly, and cost-effective method has been developed for the synthesis of α^1-oxindole-α-hydroxyphosphonate derivatives (**3a–o**) by a one-pot reaction of isatins (**1a–o**) with trialkyl phosphites (**2a–o**) under catalyst-free-conditions using inexpensive, non-toxic polyethylene glycol (PEG-400) in excellent yields (82–92%). The present methodology offers an environmental acceptability; low cost, high yields, and recyclability of the PEG-400 are the important features of this protocol.

α-Hydroxyphosphonates motifs have remarkable biological activities[1] such as antiviral, antibacterial, anticancer, and also useful as synthetic intermediates of α-substituted phosphonyl compounds.[2] In addition these derivatives are widely used in the pharmaceutical applications, such as enzyme inhibitors of rennin, EPSP synthase, and HIV protease.[3] These derivatives also show activities such as antibacterial, anti-inflammatory, laxative agents, growth hormones, and new targets for cancer chemotherapy.[4] Furthermore, these derivatives have been used in the preparation of α-ketophosphonates, α-aminophosponates, and 1,2-diketones from acid chlorides.[5]

Several different strategies for the synthesis of substituted α-hydroxy phosphonates are known, the most common protocol is the reaction of aldehydes or ketones with dialkyl or trialkyl phosphites in the presence of acidic or basic catalysts,[6,7] Meanwhile, tris(trimethylsilyl)phosphite was also used to synthesize α-hydroxy phosphonates but it requires elevated temperature under anhydrous reaction conditions.[8]

However, many of these methods are associated with various drawbacks such as use of metal catalysts, harsh reaction conditions, tedious experimental procedures, unsatisfactory yields, long reaction times, and usage of expensive and moisture sensitive catalysts. Hence, there is a need to develop a rapid, efficient, and environmentally benign synthetic protocol for the synthesis of α-hydroxyphosphonate derivatives under catalyst-free conditions.

In recent years, PEG has emerged as a powerful phase transfer catalyst and performs many useful organic transformations under mild reaction conditions. Moreover, PEG is inexpensive, easy to handle, thermally stable, non-toxic, and recyclable in various organic transformations, such as synthesis of β-amino sulfides, 2-substituted benzimidazoles, bis-benzimidazoles, 3,4-dihydropyrimidinones, β-keto sulfides, and dibenz[*b*,*f*]-1,4-oxazapine etc.[9] This inspired us to focus on the aspect of synthesis of biologically active pyrrole derivatives under catalyst free conditions by using PEG as an eco-friendly and recyclable media. In continuation of our studies toward the development of novel methodologies[10,11] herein we report for the first time synthesis of α^1-oxindole-α-hydroxyphosphonates derivatives by using PEG-400 as a recyclable medium without adding any organic solvent and catalyst. To the best of our knowledge there are no reports for the synthesis of α^1-oxindole-α-hydroxyphosphonate derivatives by using PEG-400 as a reaction medium under catalyst-free conditions (Scheme 1).

To explore the scope of this reaction for the synthesis of α^1-oxindole-α-hydroxyphosphonate derivatives, different substituted isatins were reacted with trialkyl phosphites with PEG-400 as the reaction medium (Scheme 2, Table 1). In general, all the reactions were very clean, and the α^1-oxindole-α-hydroxyphosphonate derivatives were obtained in high yields under these conditions.[12]

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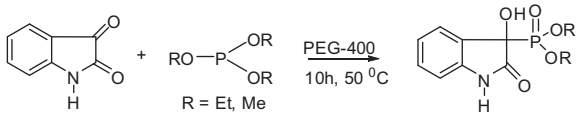
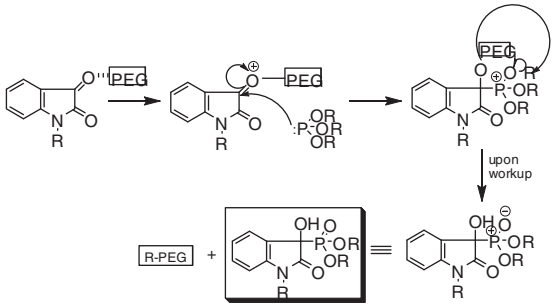
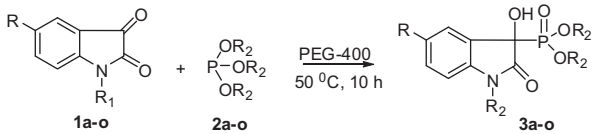


Scheme 1. PEG mediated synthesis of α^1-oxindole-α-hydroxy phosphonates.



Scheme 2. Plausible mechanism for the synthesis of α^1-oxindole-α-hydroxy phosphonates.

Table 1
PEG-400 mediated synthesis of α^1-oxindole-α-hydroxy phosphonates[a]



1a-o 2a-o 3a-o

Entry	R	R_1	R_2	Yield[b] (%)
a	H	H	Et	90
b	Me	H	Et	87
c	OMe	H	Et	89
d	F	H	Et	82
e	Cl	H	Et	85
f	Br	H	Et	87
g	NO_2	H	Et	84
h	H	Me	Et	86
i	H	Ph	Et	83
j	H	$-CH_2Ph$	Et	85
k	H	H	Me	92
l	Me	H	Me	89
m	Br	H	Me	86
n	F	H	Me	84
o	NO_2	H	Me	86

[a] Reaction conditions: Isatin (1 mmol), trialkyl phosphite (1 mmol), PEG (5 mL), 50 °C, 10 h.
[b] Isolated yields.

Isatin bearing electron-donating groups (Me, OMe) and electron-withdrawing groups (NO_2) gave the desired products in quantitative yields in 10 h (Table 1, entries b, c, q, l, o). Results show that the substituent groups did not play any significant role in the reactivity of the substrate.

In conclusion, we have developed an efficient and facile method for the synthesis of α^1-oxindole-α-hydroxyphosphonate derivatives by the treatment of the corresponding isatins with trialkyl phosphites by using PEG-400 as a recyclable medium without the addition of any additive or organic co-solvent under catalyst-free conditions. The mild reaction conditions, less expensive reaction medium, operational simplicity, and high yields are the advantages of this protocol. PEG-400 mediated reactions are very useful both from economical and environmental points of view.

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12. *General Procedure for the Synthesis of α^1-oxindole-α-hydroxyphosphonate by using PEG as the reaction medium:* A mixture of isatin (1.0 mmol) and trialkyl phosphite (1.0 mmol) was taken in 5 mL of polyethylene glycol, and stirred at 50 °C for 10 h. After completion of the reaction, as monitored by TLC, the reaction mass was poured into water and extracted into ethyl acetate. The organic layer was removed under reduced pressure, and the crude product was purified by column chromatography. The recovered PEG can be reused for a number of cycles without any significant loss of activity.
Data of representative examples:
*Diethyl 3-hydroxy-2-oxoindolin-3-ylphosphonate (*Table 1, *entry1):* Pale yellow solid; Yield 92%; mp 142–144 °C ; IR: 3201, 2987, 1730, 1621, 1473,1395 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.34–7.24 (m, 2H), 6.94–6.89 (m, 2H), 4.49–3.99 (m, 4H), 1.54–1.10 (m, 6H),; ^{13}C NMR (75 MHz,$CDCl_3$) δ 160.95, 138.61, 130.69, 125.72, 123.92, 112.44, 64.81, 63.18, 16.07, 14.1; MS *m*/*z* (ESI); 309 $[M+Na]^+$. HRMS *m*/*z* calcd for $C_{12}H_{16}NO_5NaP$ 309.1029; found 309.1027.
*Diethyl 3-hydroxy-5-methyl-2-oxoindolin-3-ylphosphonate (*Table 1, *entry 2):* brown semisolid; Yield 91%; IR: 3203, 2985, 2858, 1733, 1627, 1492, 1247, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.14 (s,1H), 7.49–7.07 (m, 2H), 6.99–6.56 (m, 1H), 4.28–3.93 (m, 4H), 3.73 (s,1H), 2.07 (s, 3H), 1.51–0.88 (m, 6H),; ^{13}C NMR (75 MHz,$CDCl_3$): δ 169.16, 138.73, 132.80, 130.90, 126.97, 110.03, 72.65, 64.61, 29.67, 20.98, 15.96; MS *m*/*z* (ESI); 322 $[M+Na]^+$. HRMS *m*/*z* calcd for $C_{13}H_{18}NO_5NaP$ 322.0820; found 322.0819.
Diethyl 3-hydroxy-5-nitro-2-oxoindolin-3-ylphosphonate(Table 1, *entry 7):* Pale yellow solid; Yield 93%; mp 144–146 °C; IR: 3179, 2991, 2114, 1751, 1627, 1523, 1342 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.44-8.18 (m, 2H), 6.97–6.88 (m,1H), 4.58–3.85 (m, 4H), 1.75–1.02 (m, 6H); ^{13}C NMR(75 MHz,$CDCl_3$): δ 170.25, 159.25, 136.29, 127.46, 122.00, 110.43, 71.79, 64.99, 29.68, 15.72; ^{31}P NMR, δ: 19.59MS *m*/*z* (ESI); 331 $[M+H]^+$. HRMS m/z calcd for $C_{12}H_{15}N_2O_7NaP$ 353.054; found 353.0500.
*Dimethyl 3-hydroxy-5-methyl-2-oxoindolin-3-ylphosphonate (*Table 1, *entry 12):* Orange oil liquid; Yield 92%; ^1H NMR (200 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.39–7.25 (m, 1H), 7.16–7.05 (m, 1H), 6.75–6.83 (m, 1H), 3.91–3.80 (m, 6H), 3.80 (s, OH), 2.29 (s, 3H); MS *m*/*z* (ESI); 318 $[M+H]^+$.