Tetrahedron Letters 51 (2010) 3938–3939

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Novel aqueous phase supramolecular synthesis of α^1-oxindole-α-hydroxyphosphonates

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ARTICLE INFO

Article history:
Received 11 March 2010
Revised 19 May 2010
Accepted 22 May 2010
Available online 26 May 2010

ABSTRACT

α^1-Oxindole-α-hydroxyphosphonates were synthesized for the first time in water under neutral conditions mediated by β-cyclodextrin in high yields. The β-cyclodextrin can be recovered and reused without any loss of activity.

α-Hydroxyphosphonates are an attractive class of biologically active compounds as well as useful synthetic intermediates of α-substituted phosphonyl compounds.[1] The synthesis of α-hydroxyphosphonates has received an increasing amount of attention due to significant biological interests. They are widely used in pharmaceutical applications, for example, as enzyme inhibitors of renin, EPSP synthase, and HIV protease.[2] They also showed potential biological activities, such as antiviral, antibacterial, and anticancer activities.[3] They have been used in the preparation of α-ketophosphonates, α-aminophosponates,[4] and 1,2-diketones from acid chlorides. Substituted oxindoles are useful as antibacterial, anti-inflammatory, laxative agents, growth hormones, and new targets for cancer chemotherapy.[5]

The most frequently used methods for the synthesis of α-hydroxyphosphonates involve the reaction of aldehydes or ketones with dialkyl or trialkyl phosphites in the presence of acidic or basic catalysts. Reactions with dialkyl phosphites involve usage of alumina, potassium fluoride on alumina, cesium fluorides, quaternary ammonium hydroxide ion exchange resin, and titanium alkoxides.[6] Reactions with trialkyl phosphites involve usage of lithium perchlorate, guanidine hydrochloride, hydrogen chloride, and Amberlyst-15 as catalysts.[7] Tris(trimethylsilyl) phosphite was also used to synthesize α-hydroxyphosphonates but it requires elevated temperature under anhydrous reaction conditions.[8] However, these methodologies also have limited scope due to the use of metal catalysts, acidic conditions, and hazardous solvents. As a consequence, the development of environmentally benign practical synthetic routes under neutral conditions for accessing these α-hydroxyphosphonates still remains a major goal. Organic reactions in aqueous media have recently become the focus in organic synthesis since they overcome the harmful effects of organic solvents and are environmentally benign. These aqueous reactions can be made more sophisticated if they can be performed under supramolecular catalysis.

In view of different biological activities associated with various oxindole derivatives and α-hydroxyphosphonates and in continuation of our interest in the use of cyclodextrins as mild and efficient biomimetic catalysts in promoting various transformations,[9] we have attempted the novel aqueous phase synthesis of α^1-oxindole-α-hydroxyphosphonates by the reaction of isatin derivatives with dialkyl or trialkyl phosphites under neutral conditions involving supramolecular catalysis using β-cyclodextrin.

Cyclodextrins (CDs) are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host-guest complexes by non-covalent bonding as seen in enzymes. We describe, herein, the first aqueous phase synthesis of α^1-oxindole-α-hydroxyphosphonates demonstrating the remarkable catalytic activity of β-cyclodextrin (Scheme 1).

In general, the reaction was carried out by the in situ formation of the β-CD complex of the isatin in water followed by the addition of dialkyl or trialkyl phosphite and stirring at rt to give the corresponding α^1-oxindole-α-hydroxyphosphonates in high yields (86–94%).[10] These reactions proceed efficiently without the need of any metal or acid catalyst. The reaction goes to completion in a short time (0.5–4 h). This methodology is also compatible with various substituted isatins and indoles. The reactions also take place with α-CD and γ-CD, with lesser yields, however, β-CD has been chosen as the mediator since it is inexpensive and easily accessible. Several examples illustrating this simple and practical methodology are summarized in Table 2. No byproduct formation was observed. β-Cyclodextrin can be easily recovered and reused. All the compounds were characterized by ^{1}H NMR, IR, and mass spectrometry.

The catalytic activity of cyclodextrins for these reactions is established by the fact that no reaction was observed in the absence of cyclodextrin. Evidence for complexation between the amine and cyclodextrin is supported by ^{1}H NMR spectroscopy. A comparison of the ^{1}H NMR spectra (D_2O) of β-CD, β-CD: isatin com-

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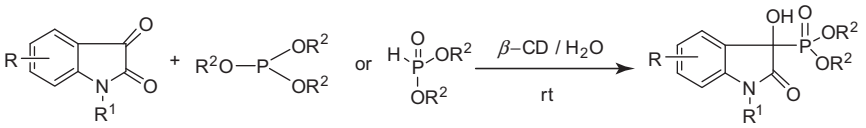
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.05.096



R=H, NO_2, Br, Cl, F, CH_3, OCH_3
R^1=H, CH_3, Ph, $PhCH_2$
R^2=Et, Me

Scheme 1.

Table 1
Recyclability of β-CD

Cycles	Yield (%)	Catalyst recovered (%)
Native	92	91
1	88	89
2	85	85
3	81	83

Table 2
β-CD-catalyzed synthesis of α^1-oxindole-α-hydroxyphosphonates

Entry	R	R^1	R^2	Time (h)	Yield (%)
1	H	H	Et	3	92
2	5-CH_3	H	Et	3.2	91
3	5-NO_2	H	Et	1	93
4	5-Br	H	Et	0.5	94
5	5-Cl	H	Et	1	91
6	5-F	H	Et	1.2	90
7	5-OMe	H	Et	4	87
8	H	CH_3	Et	1.2	92
9	H	Ph	Et	1	90
10	H	CH_2Ph	Et	1.5	89
11	H	H	Me	3	90
12	5-CH_3	H	Me	3.5	89

plex was studied. There is an upfield shift of H_3 (0.02 ppm) and H_5 (0.02 ppm) protons of cyclodextrin in the β-CD: isatin complex as compared to β-CD, indicating the formation of an inclusion complex of isatin with β-CD.[9a] The complexation with β-CD increases the reactivity of keto group of isatin due to intermolecular hydrogen bonding with the CD-hydroxyl groups facilitating the addition of phosphite. Here, β-CD not only forms the inclusion complex with isatin but is also involved in the intermolecular hydrogen bonding with the guest to promote the reaction.

β-CD was recovered and reused. After the reaction, the reaction mass was cooled to room temperature and β-CD was filtered and washed with ice-cold water and dried. The recovered β-CD was further used with the same substrates as a catalyst and checked for the yields and catalytic activity of recovered catalyst (β-CD). As shown in Table 1, the yields of α^1-oxindole-α-hydroxyphosphonates (entry 1) after two to three recycles were almost same (Table 1).

In summary, we have developed a neutral aqueous phase synthesis of various α^1-oxindole-α-hydroxyphosphonates by the reaction of the corresponding isatin with dialkyl or trialkyl phosphites under biomimetic conditions in the presence of β-cyclodextrin. These cyclodextrin-mediated aqueous phase reactions are very useful both from economical and environmental points of view. β-Cyclodextrin, apart from being nontoxic, is also considered as metabolically safe. This straightforward and environmentally benign methodology may find widespread application in organic and medicinal chemistry.

Acknowledgment

We thank CSIR, New Delhi, India, for awarding fellowships to J.S., K.K., and B.S.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.096.

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10. *General procedure for the synthesis of α^1-oxindole-α-hydroxyphosphonates*
Typical example: Synthesis of diethyl 3-hydroxy-2-oxoindolin-3-ylphosphonate (Table 2, entry 1):
β-Cyclodextrin (1.135 g, 1 mmol) was dissolved in water (15 mL) by warming to 60 °C until a clear solution was formed. Then, isatin (0.147 g, 1 mmol) dissolved in methanol (0.5 mL) was added dropwise followed by triethyl phosphate (0.199 g, 1.2 mmol) and the mixture was stirred at rt until the reaction was complete (as monitored by TLC) (Table 2). The mixture was extracted with ethyl acetate (3 × 10 mL) and the extract was filtered. The organic layer was dried over anhydrous Na_2SO_4, the solvent was removed under reduced pressure, and the resulting product was further purified by column chromatography by using ethyl acetate and hexane (7:3) as eluent to give the title compound (Table 2, entry 1) (0.262 g, 92%). The aqueous layer was cooled to 5 °C to recover β-CD by filtration.
Pale yellow solid; Yield 92%; mp 142–144 °C; R_f (70% EtOAc/*n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10–1.54 (m, 6H), 3.99–4.49 (m, 4H), 6.89–6.94 (m, 2H), 7.24–7.34 (m, 2H), 8.2 (s, 1H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 14.1, 16.07, 63.18, 64.81, 112.44, 123.92, 125.72, 130.69, 138.61, 160.95; ^{31}P NMR, δ: 21.91. IR: 3201, 2987, 1730, 1621, 1473, 1395 cm^{-1}; MS *m*/*z* (ESI); 309 $(M+Na)^+$. HRMS *m*/*z* calcd for $C_{12}H_{16}NO_5NaP$: 309.1029; found: 309.1027.