Simple and Catalyst-Free Synthesis of Oxoindolin-3-yl Phosphonates

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Received October 27, 2009

An efficient, simple, and catalyst-free synthesis of dialkyl or diaryl 3-(dicyanomethyl)-2-oxoindolin-3-ylphosphonates by the reaction of dialkyl or diaryl phosphites and oxoindolin-3-ylidenemalononitriles under solvent-free conditions is reported. The reaction of imino isatins with dialkyl or diaryl phosphites results in the formation of dialkyl or diaryl 2-oxo-3-(arylamino)indolin-3-ylphosphonates.

1. Introduction

Isatin and derivatives have been demonstrated to be versatile starting materials for the synthesis of heterocyclic and noncyclic, natural products, and analogues, as well as for the synthesis of potentially important compounds with biological activities.[1] Oxindoles are well-known among these compounds. Oxindoles are useful as antibacterial, antiflammatory, and laxative drugs.[2,3] Furthermore, this heterocyclic compounds have been isolated from plant.[4] Therefore, a number of methods have been reported for the synthesis of oxindole derivatives.[5−8]

Organophosphorus compounds have found a wide range of application in the areas of industrial, agricultural, and medicinal chemistry because of their biological and physical properties, as well as their utility as synthetic intermediates.[9−11] α-Functionalized phosphonic acids are valuable intermediates for the preparation of medicinal compounds and synthetic intermediates.[12−14] Natural products containing P−C bonds also show interesting biological activities.[15,16]

Among various methods to generate P−C bonds, the addition of P(O)−H bonds across alkenes is one of the most utilized approaches.[17] There are three general approaches: (a) the phospha-Michael reaction of activated alkenes, most commonly promoted by catalysts[17−21] or microwave irradiation,[22] (b) the addition to inactivated olefins, promoted by radical initiators,[23] and (c) the hydrophosphorylation of inactivated alkenes catalyzed by transition metals.[24,25]

The synthesis of α-amino phosphonates exhibiting high biological activity has recently attracted a lot of attention.[26] Because of their structural analogy with α-amino acids, this type of organophosphorous compounds are widely used for the development of new inhibitors of enzymes, neuroactive compounds, antibiotics, and plant-growth regulators.[27] Thus, a variety of synthetic approaches are desirable to synthesize α-amino phosphonates. Of the methods available, the nucleophilic addition of phosphites to imines is convenient and is usually activated by catalyst.[28]

Considering the above reports and as part of our program that aims to develop new selective and environmentally friendly methodologies for the preparation of heterocyclic compounds,[29] we report herein, the synthesis of oxoindolin-3-yl phosphonates by efficient and catalyst-free methods.

2. Results and Discussion

We found that a mixture of 2-(2-oxoindolin-3-ylidene)malononitriles **1a**−**f** and dialkyl or diaryl phosphites **2a**−**d** in the absence of any catalyst at 50 °C for 1.5−5 h under solvent-free conditions, afforded dialkyl or diaryl 3-(dicyanomethyl)-2-oxoindolin-3-ylphosphonates **3a**−**r** in good yields (Scheme 1). The results are summarized in Table 1. Several 2-(2-oxoindolin-3-ylidene)malononitriles carrying different substituents worked well, mostly leading to good yields of products. Another advantage of this method is its efficiency for the high yield synthesis of products from dialkyl or diaryl phosphites.

To the best of our knowledge, this new procedure provides the first example of a catalyst-free synthesis of dialkyl or diaryl 3-(dicyanomethyl)-2-oxoindolin-3-ylphosphonate derivatives. The reactions under catalyst- and solvent-free conditions are considerably safe, nontoxic, environmentally friendly, and inexpensive. The absence of catalyst for the reaction allows avoiding the use of moisture sensitive and heavy metal Lewis acids. This method, based on catalyst-free reaction under solvent-free conditions, is the most simple and convenient and would be applicable for the synthesis of different types of dicyanomethyl-oxoindolin-3-ylphosphonates.

Due to the biological importance of α-amino phosphonates, we extended the reaction of dialkyl or diaryl phosphites **2** with various imino isatins **4** under similar conditions, furnishing the respective dialkyl or diaryl 2-oxo-3-(arylamino)indolin-3-ylphosphonates **5a**−**z** in good yields (Scheme 2). The results are summarized in Table 2. The imino isatins carrying both electron-withdrawing and electron-releasing substituents were also converted to their corresponding

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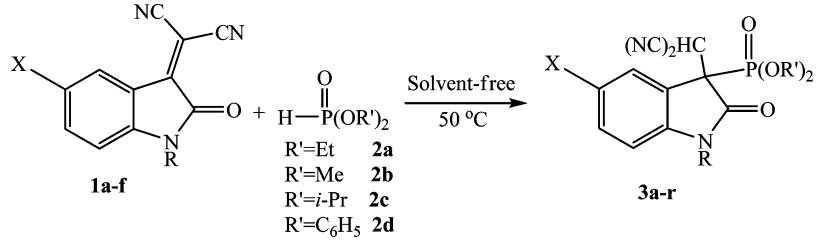
10.1021/cc900169p
Published on Web 01/28/2010

Scheme 1. Synthesis of Dialkyl or Diaryl 3-(Dicyanomethyl)-2-oxoindolin-3-ylphosphonates **3**



Scheme 2. Synthesis of Dialkyl or Diaryl 2-Oxo-3-(arylamino)indolin-3-ylphosphonates **5**

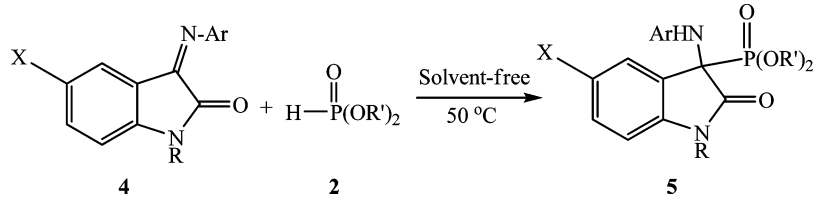


Table 1. Synthesis of Dialkyl or Diaryl 3-(Dicyanomethyl)-2-oxoindolin-3-ylphosphonates **3**

products **3**	R	X	R′	time (h)	yield (%)
a	H	H	Et	2	82
b	$PhCH_2$	H	Et	2.5	80
c	Me	H	Et	3	78
d	H	NO_2	Et	1.5	86
e	H	Br	Et	1.5	83
f	H	H	Me	2	81
g	$PhCH_2$	H	Me	1	80
h	Me	H	Me	2.5	79
i	H	NO_2	Me	2	83
j	H	Br	Me	1.5	80
k	Me	Br	Me	3	78
l	H	H	*i*-Pr	4.5	82
m	$PhCH_2$	H	*i*-Pr	3	78
n	Me	H	*i*-Pr	5	80
o	H	NO_2	*i*-Pr	2.5	84
p	H	Br	*i*-Pr	2	81
q	H	H	C_6H_5	5	80
r	H	NO_2	C_6H_5	3	86

Table 2. Synthesis of Dialkyl or Diaryl 2-Oxo-3-(arylamino)indolin-3-ylphosphonates **5**

products **5**	R	X	R′	Ar	time (min)	yield (%)
a	H	H	Et	C_6H_5	20	88
b	H	H	Et	4-Me-C_6H_4	25	88
c	H	H	Et	4-MeO-C_6H_4	20	91
d	H	H	Et	4−Cl-C_6H_4	15	87
e	H	H	Et	4-NO_2−C_6H_4	30	88
f	H	H	Et	4-Et-C_6H_4	30	90
g	H	H	Et	4−Br-C_6H_4	20	95
h	Me	H	Et	4-Me-C_6H_4	50	90
i	Me	H	Et	4-MeO-C_6H_4	70	89
j	Me	H	Et	4−Cl-C_6H_4	60	88
k	Me	H	Et	4−Br-C_6H_4	50	86
l	$PhCH_2$	H	Et	4-Me-C_6H_4	95	87
m	$PhCH_2$	H	Et	4−Cl-C_6H_4	100	89
n	$PhCH_2$	H	Et	4-MeO-C_6H_4	100	88
o	$PhCH_2$	H	Et	4-NO_2−C_6H_4	80	90
p	H	Br	Et	4−Cl-C_6H_4	100	89
q	H	Br	Et	4-Me-C_6H_4	90	85
r	H	Br	Et	4-MeO-C_6H_4	110	91
s	H	H	Me	4−Cl-C_6H_4	100	91
t	$PhCH_2$	H	Me	4-MeO-C_6H_4	85	95
u	$PhCH_2$	H	Me	4-Me-C_6H_4	70	94
v	Me	H	*i*-Pr	4-Me-C_6H_4	80	90
w	H	H	*i*-Pr	C_6H_5	100	78
x	H	H	C_6H_5	C_6H_5	90	89
y	H	H	C_6H_5	4-Me-C_6H_4	60	97
z	H	Br	C_6H_5	4-Me-C_6H_4	70	96

dialkyl or diaryl 2-oxo-3-(arylamino)indolin-3-ylphosphonate derivatives in relatively similar times and yields (Table 2).

The workup of these very clean reactions involves only a simple washing step (diethyl ether) to remove unreacted starting materials. For further purification, the residue recrystallized from EtOH-H_2O. Using this simple purification protocol the desired products are obtained in high purity. Compounds **3** and **5** are stable solids whose structures were established by IR, ^1H, ^{31}P and ^{13}C NMR spectroscopy, mass spectrometry and elemental analysis.

In conclusion, an efficient, atom-economical, and simple method for the preparation of dialkyl or diaryl 3-(dicyanomethyl)-2-oxoindolin-3-ylphosphonates and dialkyl or diaryl 2-oxo-3-(arylamino)indolin-3-ylphosphonates using readily available starting materials under solvent-free conditions was reported. Prominent among the advantages of this new catalyst-free method are the operational simplicity, good yields, and the easy workup procedures employed.

3. Experimental Section

General Procedure for the Preparation of Oxoindolin-3-yl Phosphonates. A mixture of 2-(2-oxoindolin-3-ylidene)malononitrile or imino isatin (1 mmol) and dialkyl or diaryl phosphite (1.1 mmol) was stirred at 50 °C for an appropriate time (Table 1 and Table 2). After completion of reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (5 mL) and residue recrystallized from EtOH-H_2O (1:3) to afford the pure product.

Acknowledgment. We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

Supporting Information Available. Experimental procedures and IR, ^1H NMR, and ^{13}C NMR spectra for compounds **3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC900169P