Tetrahedron Letters 58 (2017) 2997–3001

Contents lists available at ScienceDirect

Tetrahedron Letters

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

$BF_3{\cdot}Et_2O$ catalyzed intramolecular cyclization of diethyl 2-(dialkoxyphosphorylethynyl)-2-arylaminomalonates to 3-phosphonylated indoles

Anastasia V. Egorova [a], Nikolai B. Viktorov [a], Galina L. Starova [b], Nataly I. Svintsitskaya [a,*], Aleksandr V. Garabadziu [a], Albina V. Dogadina [a]

[a] Saint-Petersburg State Institute of Technology (Technical University), Moskovskii pr. 26, Saint Petersburg 190013, Russia
[b] Saint-Petersburg State University, Universitetskii pr. 26, Saint Petersburg 198504, Russia

ARTICLE INFO

Article history:
Received 7 May 2017
Revised 16 June 2017
Accepted 20 June 2017
Available online 21 June 2017

Keywords:
Phosphorylated indoles
Phosphonylated indoles
Aminomalonates
Phosphonylated 2-arylaminomalonic esters
Decarboxylation

ABSTRACT

The boron trifluoride diethyl etherate catalyzed intramolecular cyclization of diethyl 2-(dialkoxyphosphorylethynyl)-2-arylaminomalonates afforded a series of novel 3-phosphonylated indoles, diethyl 2-[3-(dialkoxyphosphoryl)-1*H*-indol-2-yl]propanedioates. Decarboxylation of the latter compounds resulted in the formation of ethyl 2-[3-(dialkoxyphosphoryl)-1*H*-indol-2-yl]acetates.

The indole motif is present in a large number of important naturally occurring compounds that exert considerable pharmacological activities; for example as plant growth regulators, neurotransmitters, amino acids, and antibiotics.[1,2] Indole derivatives are also very important heterocyclic compounds in drug discovery. Thus, indole-based medications are widely used for the treatment of cardiovascular and neurological diseases as well as analgesic and hemostatic agents.[3] Additionally, indole derivatives have found broad application as dyes and pigments, antioxidants, fragrances, co-monomers, nutraceuticals, and dietary supplements.[4]

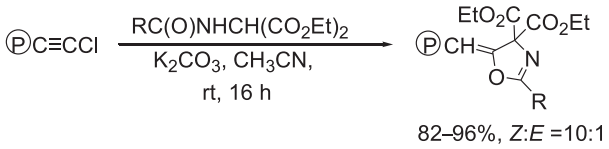
The introduction of organophosphorus functional groups to the indole skeleton has been used to increase or create new biological activities. Recently, 3-phosphonylated indoles have been reported as good inhibitors against HIV-1;[5] hence the development of novel approaches towards phosphoindoles has become increasingly important. Very few routes towards phosphorus-containing indoles have been reported,[6] mostly concerning indoles substituted with phosphorus groups at the 2- or 3-position of the azole ring together with a much smaller number bearing a phosphorus moiety on the benzene ring. Since indoles are widely available, direct *C*-phosphorylation[7] represents an efficient strategy for the synthesis of different types of phosphoindoles. A prominent early method for the synthesis of phosphorylated indoles was the Fischer cyclization.[8] Conceptually new approaches for the synthesis of phosphoindoles involving the palladium-catalyzed annulation of 1-alkynylphosphine sulfides with 2-iodoanilines or the palladium-assisted reaction of *o*-(2,2-dibromovinyl)aniline with dialkyl phosphite have been developed by the groups of Yorimitsu[9] and Bisseret.[10]

Extending the chemistry of chloroethynylphosphonates, we recently reported their reactions with amidomalonates in an effort to obtain novel phosphonylated heterocycles.[11] The reactions proceeded *via* initial alkynylation of the malonate and subsequent reaction of the nucleophilic carbonyl site with the acetylene bond in the presumed intermediate to give the oxazoline ring (Scheme 1). The reaction of chloroethynylphosphonates with diethyl 2-aminomalonate also involved intramolecular cyclization, resulting in the formation of phosphorylated heterocycles.[12]

Additionally, our group also reported the reaction of chloroethynylphosphonates with *N*-arylated diethyl 2-aminomalonates (Scheme 2). The reaction occurred as a *C*-nucleophilic substitution of the triple bond chlorine atom,[13] affording the

* Corresponding author.
E-mail address: nsvincickaya@mail.ru (N.I. Svintsitskaya).

http://dx.doi.org/10.1016/j.tetlet.2017.06.062
0040-4039/



Ⓟ = P(O)(OAlk)$_2$; R = Me, Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$.

Scheme 1. Reaction of chloroethynylphosphonates with 2-amidomalonates.

corresponding 2-(dialkoxyphosphorylethynyl)-2-arylaminomalonates in good yields.[14] In this core, the cyclization reaction demonstrated for amidomalonates[11] and the unsubstituted aminomalonate[12] was not observed.

Despite the fact that ethynylphosphonates **1** were found to be less reactive in the described cyclization processes, they were recognized as unusual starting materials for the preparation of phosphoindoles. Due to the high polarization of the acetylene fragment, the *N*-nucleophilic site can be involved in an intramolecular cyclization reaction similar to that previously described.[11,12] Various catalysts including Pd(OAc)$_2$, KOAc, K$_2$CO$_3$, KF, *t*-BuOK and selected Lewis acids (AlCl$_3$, CuCl, ZnCl$_2$, BF$_3$·Et$_2$O) were screened. Among these catalysts boron trifluoride diethyl etherate was the most effective; the intramolecular cyclization proceeded selectively to afford only the indole product. In order to examine the reaction scope, compounds **1a–i** in anhydrous benzene were heated at reflux in the presence of BF$_3$·Et$_2$O for 5–8 h to afford 3-phosphonylated indoles **2a–i** in good yields[15] (Table 1, Scheme 3).

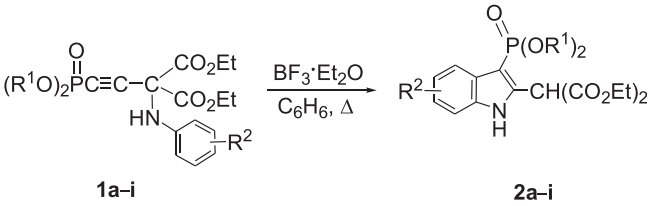
The reaction progress was monitored by ^{31}P NMR spectroscopy; disappearance of the signal for ethynylmalonate **1** between δ_P −4.84 and −8.55 ppm and the appearance of a new signal between δ_P 14.96 and 19.47 ppm belonging to the product was indicative of reaction completion. The obtained compounds were isolated by column chromatography and purified by recrystallization from isooctane. Note that dimethyl phosphonates are difficult to isolate by column chromatography or recrystallization due to ready cleavage of one alkyl group of the dialkoxyphosphoryl fragment with formation of a monophosphonate. The 3-phosphonylated indoles **2a–i** are crystalline substances which are readily soluble in common solvents (Table 1).

The structure of phosphoindoles **2a–i** were confirmed using ^{1}H, ^{13}C, ^{31}P, and ^{15}N NMR spectroscopy.[16] The ^{31}P chemical shift of phosphonates **2a–i** (14.96–19.47 ppm) was typical of phosphonates with an *sp*^{2}-hybridized carbon atom. The ^{1}H NMR spectrum of the phosphoindoles **2a–i** contained characteristic signals from non-equivalent alkoxy groups of the malonate and phosphoryl fragments; the phenyl protons resonated at the lowest field. The malonate CH-proton was observed between 6.16 and 6.23 ppm while the NH-proton of the indole ring resonated between 9.42 and 9.98 ppm. The ^{13}C NMR spectrum contained doublet signals for the C^3 and C^2 carbon atoms of the indole ring between 98.83–105.62 ppm and 127.92–129.75 ppm, exhibiting typical spin-spin coupling constants of $^{1}J_{CP}$ 212.7–214.6 Hz and $^{2}J_{CP}$ 10.8–11.4 Hz, respectively. The doublet signal at 138.15 ppm ($^{1}J_{HN}$ 100.7 Hz) observed in the ^{15}N NMR spectrum of **2d** also

Table 1
3-Phosponylated indoles **2a–i**.[a]

Product	R^1	R^2	Time (h)	Yield[b] **2** (%)
2a	CH$_3$	H	5	92 (72)
2b	C$_2$H$_5$	H	6	89 (76)
2c	C$_2$H$_5$	7-CH$_3$	7	85 (72)
2d	C$_2$H$_5$	6-CH$_3$	6	82 (70)
2e	C$_2$H$_5$	5-CH$_3$	5	91 (71)
2f	C$_2$H$_5$	5-OCH$_3$	5	83 (65)
2g	C$_2$H$_5$	5-Br	8	86 (68)
2h	C$_2$H$_5$	5-F	8	83 (65)
2i	C$_2$H$_5$	5-Cl	8	88 (67)

[a] Reagents and conditions: ethynylmalonate (0.025 mol), BF$_3$·Et$_2$O (5–15 mol%), benzene (25 mL), reflux.
[b] Determined by 31P NMR, isolated yield (column chromatography) given in brackets.



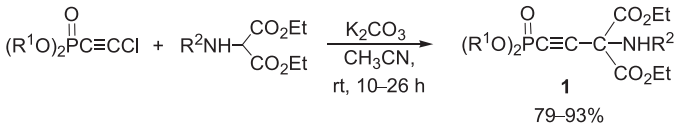
Scheme 3. Synthesis of diethyl 3-(dialkoxyphosphoryl)-1*H*-indole-2-malonates **2a–i**.

allowed clear identification of the indole derivatives. Signal assignment was made using heteronuclear ^{1}H–^{13}C HMQC and ^{1}H–^{13}C HMBC techniques.

Single crystal X-ray diffraction data of 1,3-diethyl 2-[3-(diethoxyphosphoryl)-5-bromo-1*H*-indol-2-yl]propanedioate **2g**[17] unambiguously confirmed the formation of 3-phosphonylated indole-2-malonate (Fig. 1).

A plausible mechanism for the intramolecular cyclization of diethyl 2-(dialkoxyphosphorylethynyl)-2-arylaminomalonates **1** is proposed in Scheme 4. Initially boron trifluoride diethyl etherate coordinates to the oxygen atom of the P=O group to give the phosphorylide structure with enhanced electrophilicity of the alkyne carbon atom. Coordination of BF$_3$·Et$_2$O to the nitrogen atom can also be considered. However, according to quantum-chemical estimates performed for the reactions of (dialkylaminoethynyl)phosphonates with amines,[18] aromatic amines are inactive in the formation of adducts with BF$_3$·Et$_2$O, and coordination with the phosphoryl group is preferred. Further attack of the electrophilic carbon atom onto the activated *ortho*-carbon of the aminoaryl moiety leads to the probable formation of dihydroquinoline intermediate **A**. Further aromatization of presumed intermediate **A** affords the target 3-phosphonylated indoles **2**. A similar rearrangement of dihydroquinolines to indoles has been previously reported.[19,20]

Malonic acid esters readily undergo decarboxylation, and elimination of one ester group in phosphoindoles **2e**, **2g** and **2h** following the protocol of Johnson and co-workers[21] afforded novel indoles, 3-(dialkoxyphosphoryl)-1*H*-indole-2-acetates **3a–c** in 72–76% yield (Scheme 5).



R^1 = Me, Et; R^2 = Ph, 4-MeC$_6$H$_4$, 2-MeC$_6$H$_4$, 3-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-FC$_6$H$_4$.

Scheme 2. Reaction of chloroethynylphosphonates with arylaminomalonates.