Short communication

Synthesis of 3-Phenyl-2,1-benzisoxazoles *via* Conversion of Diethyl α-(o-Nitroaryl)benzylphosphonates

Daniel Sulikowski and Mieczysław Mąkosza

Institute of Organic Chemistry PAS, ul. Kasprzaka 44/52 01-224 Warszawa, Poland

** Corresponding author: E-mail: icho-s@icho.edu.pl*
Fax: 0048 22 632 66 81

Received: 24-10-2008

Dedicated to Professor Branko Stanovnik on the occasion of his 70th birthday

Abstract

Diethyl α-(o-nitroaryl)benzylphosphonates readily available *via* ONSH reaction upon treatment with base undergo cyclization leading to 3-phenyl-2,1-benzisoxazole in high yields. Possible route for this transformation is discussed.

Keywords: Benzisoxazoles, cyclization, heterocycles, nitroarenes, phosphonates

1. Introduction

2,1-Benzisoxazoles (anthranils) form an important class of heterocyclic compounds having 10π-electron system. Due to multifacial reactivity, they are used as versatile intermediates in organic synthesis[1]and also as biologically active compounds acting as anti-inflammatory agents[2] and glucohydrolase inhibitors.[3] Their wide use in organic synthesis is a result of high susceptibility to reducing and oxidizing agents, thus they are intermediates in synthesis of *o*-amino- and *o*-nitrobenzophenones,[4] the former are key educts in manufacturing benzodiazepines and other important heterocyclic systems.[5] Furthermore, anthranils are susceptible to reaction with electrophiles[6a] and active in photochemical transformations to form azepine or acridanone derivatives.[6b]

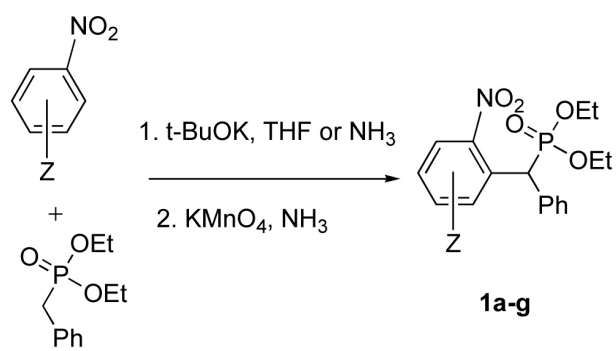
Due to these properties of benzoxazoles, their synthesis has been of considerable interest. Perhaps, the simplest and the most efficient is method reported by Davis – reaction of arylacetonitriles with nitroarenes in the presence of KOH in aqueous alcohols.[7] This method is however limited to nitroarenes bearing electron-withdrawing substituents in *para*-position. Wróbel has presented an alternative version of this reaction that is carried out in aprotic solvents in the presence of Lewis acid and DBU.[8]

Anthranils can be also produced *via* reduction o-nitrobenzoyl[9a] or *o*-nitrosobenzoyl[9b] compounds, dehydratation of *o*-nitrotoluenes[9c] and others.[9d]

2. Results and Discussion

In this communication we wish to present new efficient way for synthesis of 3-phenyl-2,1-benzisoxazoles from diethyl α-(*o*-nitroaryl)benzylphosphonates **1a–g**.

During our studies on oxidative nucleophilic substitution of hydrogen (ONSH) in nitroarenes with carbanions,[10] we have recently developed an efficient synthesis of series α-(*o*- and *p*-nitroaryl)benzylphosphonates of via ONSH in nitroarenes with carbanion of diethyl benzylphopshonate (Scheme 1).



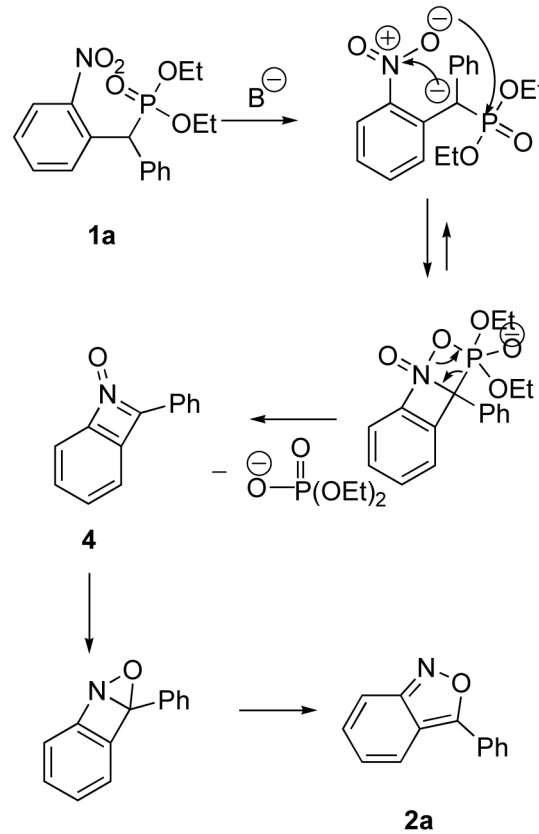
Scheme 1. Synthesis of α-(o- and p-nitroaryl)benzylphopshonates.

Using appropriate conditions we can direct this reaction selectively *ortho* to the nitro group, thus produce convenient starting material for synthesis of anthranils.[11]

Treatment of a solution of appropriate phosphonate **1a-g** with 1.1 equiv. of t-BuOK in THF at –30 °C resulted in formation of dark-coloured mixture, indicating formation of the nitrobenzylic anion. Reaction must be kept under protective atmosphere of argon, otherwise some amounts of *o*-nitrobenzophenone derivative is formed. Bubbling air through solution of anion of **1f** gave 5-methoxy-2-nitrobenzophenone in nearly quantitative yield. The mixture was allowed to reach slowly RT and kept at this temp., till the reaction was complete. Disappearing of the deep colour indicates completing of the reaction. It should be mentioned, that rate of the reaction is strongly affected by nature of substituents in the nitroaromatic ring, reaction of **2b** or **2f** is completed within 1 h, while the reaction of **2c** needs about 7 d. After standard work-up products may be isolated by column chromatography or simple recrystallization (Scheme 2). Results of the reaction with other phosphonates are presented in Table 1. Majority of benzisoxazoles produced in this work were reported earlier. Their physicochemical data are identical with those reported.

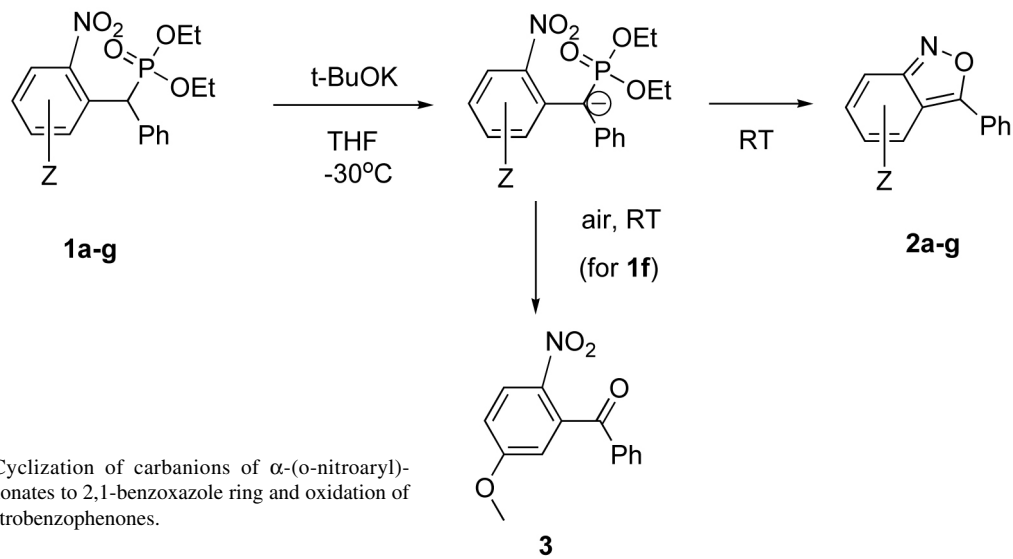
Table 1.

Substrates		Products				
Z		Z		Yields [%]	m.p. [°C]	Lit. m.p. [°C]
H	**1a**	H	**2a**	79	51–52	53–55[8]
3-Cl	**1b**	7-Cl	**2b**	71	89–90	–
4-NO_2	**1c**	6-NO_2	**2c**	43	173–174	174–175[12]
5-F	**1d**	5-F	**2d**	80	94–95	96–97[13]
5-Cl	**1e**	5-Cl	**2e**	85	114–115	116–117[8]
5-OMe	**1f**	5-OMe	**2f**	80	80–81	–
4-CN	**1g**	6-CN	**2g**	82	171–172	173–174[8]



Scheme 3. Hypothetical way of formation of 2,1-benzisoxazole system.

On Scheme 3 we present hypothetical way of transformations of α-(o-nitroaryl)-benzylphosphonates into 3-phenyl-2,1-benzisoxazoles. We suppose, that in the first step, stabilized ylide attacks nitrogen atom of the nitro group producing an intermediate analogous to that involved in the Horner-Wadsworth-Emmons reaction, which after elimination of diethyl phosphorane anion gives 3-phenyl-



Scheme 2. Cyclization of carbanions of α-(o-nitroaryl)-benzylphopshonates to 2,1-benzoxazole ring and oxidation of anions to o-nitrobenzophenones.

benzo[b]azete oxide (**4**). The later rearranges to benzisoxazole ring. Intermediacy **4** of has already been postulated on the way of pyrolytic transformation of 4-phenyl-1,2,3-benzotriazine 3-oxide in 2,1-benzisoxazoles.[14]

3. Conclusions

We have reported a new approach to the synthesis of 3-phenyl-2,1-benzisoxazoles staring from diethyl α-(o-nitroaryl)-benzylphosphonates that can be easily obtained via ONSH in nitroarenes with carbanion of diethyl benzylphosphonate. Our method provides easy access to 3-phenyl-2,1-benzisoxazoles that can contain substituents in any position of the ring. We proposed also a hypotethical route of transformation leading from phosphonate **1a-g** to 3-phenyl-2,1-benzisoxazoles, postulating formation of benzo[*b*]azete oxide as an intermediate.

4. Experimental

4. 1. General remarks

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz using $CDCl_3$ as a solvent. Chemical shits are given in ppm relative to TMS as an internal standard, coupling constant *J* are given in Hertz. Electron impact mass spectra were recorded with an AMD 604 Inectra GmbH at 70 eV, Electron-spray mass spectra were recorded with Mariner^{TM}. THF was distilled over potassium benzophenone ketyl. Silica gel Merck 60 (230–400 mesh) was used for column chromatography.

4. 2. General procedure for the synthesis of 2a-f

To a stirred solution of appropriate phosphonate (**2a-f**) (1.0 mmol) in THF (10 mL) cooled to –30 °C under argon atmosphere, 1.0 M solution of potassium *tert*-butoxide in THF (1.1 mL, 1.1 mmol) was added dropwise. Resulted dark solution was then allowed to reach RT. Progress of the reaction was monitored by TLC. After the reaction was finished, the reaction mixture was quenched with water, extracted with ethyl acetate, organic phase was dried with anhydrous magnesium sulfate and concentrated in vacuo. Solid residue was purified by column chromatography and recrystallized from methanol.

4. 3. Oxidation of carbanion 1f with air

To the stirred solution on **1f** (379 mg, 1 mmol) in THF (10 mL) cooled to –30 °C, 1.0 M solution of *tert*-BuOK in THF (1.5 mL. 1.5 mmol) was added. Dry air was passed through the reaction mixture that was allowed to reach RT. After about 20 min, when deep blue colour disappeared, solvent was evaporated, and the residue was chromatographed on silica gel (hexane/ethyl acetate) giving 5-methoxy-2-nitrobenzophenone as an yellow, solidifying oil, 234 mg, 92% yield.

4. 4. Selected analytical data

7-chloro-2,1-benzisoxazole (2b). Yield 71%, mp 89–90 (MeOH). ^{1}H NMR (400 HMz, $CDCl_3$): δd 8.02 (2H, dt, *J* = 6.8, 1.7), 7.74 (1H, dd, *J* = 8.8, 0.6), 7.60–7.52 (3H, m), 7.37 (1H, dd, *J* = 7.0, 0.6), 7.02 (1H, dd, *J* = 8.8, 7.0). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 155.1, 130.8, 129.8, 129.4, 127.7, 126.8, 126.1, 124.8, 119.5, 115.5; EI (m/z, %) : 229 (100), 194 (90), 166 (59), 164 (12), 140 (10), 139 (12), 77 (33).

5-methoxy-2,1-benzisoxazole (2f). Yield 80%, mp 80–81 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (2H, dd, J = 8.4, 1.3), 7.57–7.51 (3H, m), 7.47–7.43 (1H, m), 7.05 (1H, dd, *J* = 9.5, 2.2), 6.86 (1H, d, J = 1.8), 3.88 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1, 156.7, 156.0, 129.5, 129.2, 128.8, 127.7, 126.1, 117.0, 114.3, 94.1, 55.4. ESI(+): 226 $[MH]^+$. Anal. Calcd. for $C_{14}H_{11}NO_2$: C 74.65, H 4.95, N 6.33, N 6.22. Found: C 74.60, H 4.99

5-methoxy-2-nitrobenzophenone (3).[15] ^{1}H NMR (500 HMz, $CDCl_3$): δ 8.25 (1H, d, *J* = 9.2), 7.77–7.74 (2H, m), 7.60–7.56 (1H, m), 7.47–7.42 (2H, m), 7.08 (1H, dd, *J* = 9.2, 2.8), 3.92 (3H, s). ^{13}C NMR (125 HMz, $CDCl_3$): δ 193.1, 164.2, 139.5, 138.9, 135.9, 133.7, 129.1, 128.8, 127.0, 115.3, 113.4, 56.3. EI (m/z, %): 257 (12), 211 (17), 164 (90), 139 (13), 134 (11), 106 (16), 105 (100), 77 (45). HRMS–EI (*m/z*): $[M]^+$ calcd for $C_{14}H_{11}NO_4$, 257.07313; found, 257.06881.

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Povzetek

Dietil α-(*o*-nitroaril)benzilfosfonati so sintezno dostopni iz *o*-nitroarenov in dietil benzilfosfonata z oksidativno nukleofilno substitucijo vodika (ONSH). Opisane so ciklizacije omenjenih fosfonatov v prisotnosti baze, ki vodijo do do 3-fenil-2,1-benzizoksazolov.