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A Facile Preparation of Dialkyl Phosphonate Compounds from Sterically Hindered *p*-Nitrocumyl Halides through the $S_{RN}1$ Mechanism

Jong Uk Rhee,*,# Glen A. Russell, and Woonphil Baik[1]*

Department of Chemistry, Iowa State University, Ames, Iowa 50011
[1]Department of Chemistry, Myong Ji University, Yong In, Kyung Ki Do, 449-728, Korea

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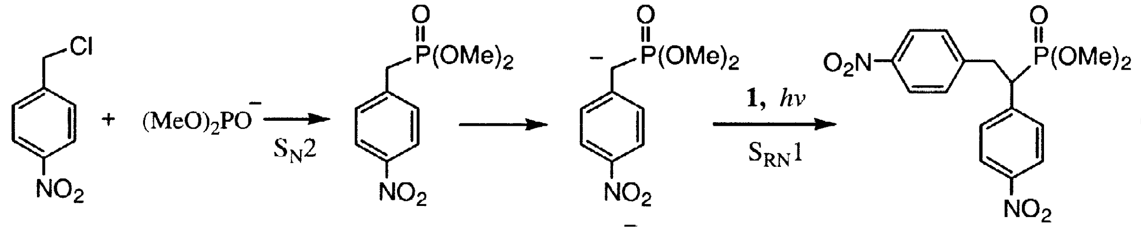
Abstract: *p*-Nitrobenzyl phosphonate anion with *p*-nitrocumyl halides gives a good yield of the coupling product dialkyl[(1,1-dimethyl-1,2-di-(*p*-nitrobenzyl)ethyl] phosphonates through the $S_{RN}1$ mechanism. The reaction was greatly accelerated by sunlamp irradiation but inhibited by the radical scavenger $(t\text{-Bu})_2NO^{\bullet}$. © 1998 Elsevier Science Ltd. All rights reserved.

It is well known that phosphorus is widely present in natural compounds. There are enormous possibilities for structural variation of these compounds with potential biological activity.[1] In particular, phosphonate derivatives exhibit significant pharmaceutical [1a] and phytopharmaceutical activities.[1b] More recently, nucleobase modified phosphonates like phosphonomethoxyethoxy adenine (PMEA, a promising anti-HIV agent) have received great attention.[1c] For new CC bond formation in phosphonate derivatives, nucleophilic substitution reactions with a variety of P(O)-stabilized carbanions have generally been employed.[1,2] Although several methods for the synthesis of phosphonates have so far been elaborated, the application of a radical based approach has not been well established. Balczewski, et al. reported that α-phosphoryl radicals generated from the α-phosphoryl halides, sulfide, or selenide with n-Bu_3SnH under the general reductive conditions react with electron rich alkenes to give the coupled phosphonate compounds.[3] A general limitation for alkenes, such as unsubstituted electron rich alkenes, has been encountered in the α-phosphoryl radical addition reactions. Recently, we have reported that the photostimulated reaction of *p*-nitrobenzyl chloride **1** with dialkyl phosphite anion $(RO)_2PO^-$ involves the formations of p-nitrobenzyl phosphonate **2** and dialkyl[(1,2-di-(*p*-nitrobenzyl)ethyl] phosphonate **3**.[4]



1 **2** **2⁻** **3** (1)

This paper is dedicated to the late Professor Glen A. Russell. Deceased on Jan. 1, 1998.

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The reactions of *p*-nitrobenzyl halides with easily oxidized carbanions A^- derived from nitroalkane give the cross coupling product as shown in Scheme 1.[5] Dialkyl phosphite anions are also known to participate as nucleophiles in the aliphatic $S_{RN}1$ mechanism.[6] However, *p*-nitrobenzyl chloride with dialkyl phosphite anions

Scheme 1. $S_{RN}1$ substitution mechanism

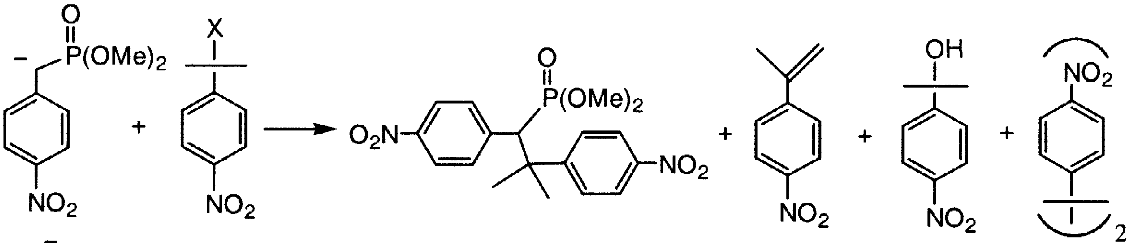
$$1^{-\bullet} \longrightarrow p\text{-}O_2NC_6H_4CH_2\bullet + Cl^-$$

$$p\text{-}O_2NC_6H_4CH_2\bullet + A^- \longrightarrow \left[p\text{-}O_2NC_6H_4CH_2\text{-}A\right]^{-\bullet}$$

$$\left[p\text{-}O_2NC_6H_4CH_2\text{-}A\right]^{-\bullet} + 1 \rightleftharpoons p\text{-}O_2NC_6H_4CH_2\text{-}A + 1^{-\bullet}$$

appear to be formed in DMSO by the S_N2 reaction (Eq. 1). Thus, it seems that dialkyl phosphite anions participate in either the $S_{RN}1$ mechanism or the S_N2 reaction depending upon the substrate employed. Meanwhile **3** is formed from **1** and **2**$^-$ mainly by the photostimulated $S_{RN}1$ mechanism. We continued these studies because the P(O)-stabilized carbanion is capable of acting as an electron donor for the aromatic electron transfer process to give the cross coupling product. In addition, the sterically hindered *p*-nitrobenzyl halides, such as *p*-nitrocumyl halides **4**, can be better candidates for generating the stabilized benzylic radical furnished by dissociation of the corresponding radical anion. We have now extended these reactions to the P(O)-stabilized carbanion and *p*-nitrocumyl halides **4** as the substrate.

Dimethyl-*p*-Nitrobenzyl phosphonate anion **2**$^-$ generated in DMSO by reaction with n-BuLi was allowed to react with *p*-nitrocumyl halides **4** under three different conditions: (**a**) ordinary laboratory lighting at 25 °C, (**b**) with 10-15% of $(t\text{-Bu})_2NO^\bullet$ present, and (**c**) with fluorescent sunlamp (275W) irradiation at 35-40 °C. The results of



2$^-$ **4** **5** **6** **7** **8**

(2)

these reactions are summarized in Table 1. Under the ordinary lighting condition for 10 min (condition **a**), the reaction of $O_2NC_6H_4CH[P(O)(OMe)_2]^-$ **2**$^-$ with $O_2NC_6H_4C(CH_3)_2Cl$ **4a** gave 10% of the cross coupling product **5**, 12% of $O_2NC_6H_4C(CH_3){=}CH_2$ **6**, and 74% of $O_2NC_6H_4C(CH_3)OH$ **7** (entry 1). The formation of $O_2NC_6H_4C(CH_3){=}CH_2$ **6** can be explained by the E_2 mechanism in which $O_2NC_6H_4CH[P(O)(OMe)_2]^-$ acts as a base. The unreacted $O_2NC_6H_4C(CH_3)_2Cl$ **4a** was readily hydrolyzed to $O_2NC_6H_4C(CH_3)_2OH$ **7** during the acidic work-up. After sunlamp irradiation for 10 min (condition **c**), the yield of the cross coupling product **5** was significantly increased to 29%, while 4% of **6** and 4%of bi-α-*p*-nitrocumyl **8** were also formed along with 61% of **7** (entry 3). If one focuses attention on the formation of **8**, it is worth commenting that this result indicates the existence of radical intermediate $O_2NC_6H_4C(CH_3)_2^\bullet$. In fact, the dimerization of the stabilized *p*-nitrobenzyl radical generated from the dissociation of *p*-nitrobenzyl halide radical anions is commonly encountered as a side reaction in photostimulated $S_{RN}1$ mechanism.[4-6] In order to obtain more reliable evidence for the existence of radicals in the reaction, the radical trapping experiment was carried out. The reaction with 10 mol% of di-*tert*-butyl nitroxide[7] showed a strong inhibitory effect on the formation of the cross coupling product **5** and the dimer of *p*-nitrocumyl radical, bi-α-*p*-nitrocumyl **8**. In fact, under the radical inhibitory condition (**condition b**), **5** and **8** were not formed at all even through a prolonged reaction time of 3 h; the elimination product **6** and the hydrolyzed product **7** were monitored in respective yields of 13% and 87% (entry 5). After a prolonged reaction time of 3 h under condition **a**, the yield of **5** was increased up to 56% with a considerable amount of bi-α-*p*-nitrocumyl **8** (entry 4). Furthermore, the reaction was greatly accelerated by photolysis to give 90% of **5** along with 5% of bi-α-*p*-nitrocumyl **8** (entry 6). In this condition, we observed a trace amount of the elimination product **6**. In a similar fashion the yield of **5** from *p*-nitrocumyl bromide **4b** with $O_2NC_6H_4CH[P(O)(OMe)_2]^-$ **2**$^-$ in DMSO (3 h, 35 °C) was 80% with sunlamp irradiation but only 6% in the dark with 10 mol% of di-*tert*-butyl nitroxide (entries 11 and 12), while in THF no reaction occurred under any conditions (entries 13-15). Even though the reactions demonstrated a great solvent effect, similar results were obtained by use of $KOMe_3$ or n-BuLi in DMSO.

Table 1. The reactions of **2**$^-$ with *p*-nitrocumyl halides **4** under three different conditions.

Entry	4	conditions[a]	time	Products (% yield)[b]				
				5	**6**	**7**	**8**	(**2**)[c]
1	**4a, X=Cl**	**a**	10 min	10	12	74	tr	(72)
2	**4a, X=Cl**	**b**	10 min	0	10	90	0	(91)
3	**4a, X=Cl**	**c**	10 min	29	1	61	4	(63)
4	**4a, X=Cl**	**a**	3 h	56	11	20	6	(31)
5	**4a, X=Cl**	**b**	3 h	0	13	87	0	(83)
6	**4a, X=Cl**	**c**	3 h	90	1	0	5	(tr)
7	**4b, X=Br**	**a**	10 min	31	11	52	0	(60)
8	**4b, X=Br**	**b, dark**	10 min	0	22	73	0	(68)
9	**4b, X=Br**	**c**	10 min	32	4	54	5	(60)
10	**4b, X=Br**	**a**	3 h	74	11	8	5	(4)
11	**4b, X=Br**	**b, dark**	3 h	6	10	25	2	(12)
12	**4b, X=Br**	**c**	3 h	80	4	6	4	(4)
13	**4b, X=Br**	**a/THF**	3 h	0	0	83 (16)[d]	0	(49)
14	**4b, X=Br**	**b/THF**	3 h	0	0	43 (43)[d]	0	(27)
15	**4b, X=Br**	**c/THF**	3 h	0	0	65 (32)[d]	0	(49)

[a] Reactions were conducted under three different conditions; **condition a** =ordinary laboratory light at 25 °C, **condition b** =with 10 mol% of di-tert-butyl nitroxide under the laboratory light or dark at 25 °C, **condition c** =250 W sun lamp irradiation at 35 °C. [b] Yields were measured by ^{1}H NMR integration and GLC. [c] The recovered starting material **2**. [d] The recovered starting material **4b**.

From these results, a few conclusions can be drawn. Photolysis promotes the formation of the cross coupling product **5**, while the presence of $(t\text{-Bu})_2NO^\bullet$ considerably prevents the formation of **5** and **8**. Compound **6** is formed in the presence or absence of $(t\text{-Bu})_2NO^\bullet$, but the yield is not increased by lengthening reaction time. The formation of bi-α-*p*-nitrocumyl **8** also implies that this reaction involves the existence of *p*-nitrocumyl radical. A significant recovery of **7** was observed only in reactions inhibited by $(t\text{-Bu})_2NO^\bullet$. On the basis of product analyses and the results of control experiments, the S_N2 mechanism can be excluded from the possible reaction pathway, meanwhile, the $S_{RN}1$ mechanism deserves serious consideration when explaining the formation of the cross coupling product **5** and the dimer **8**. Thus, one possible sequence is an electron transfer from **2**$^-$ to **4** followed by bond scission of $O_2NC_6H_4C(CH_3)_2Cl^{-\bullet}$ to form the stabilized *p*-nitrocumyl radical. The resulting *p*-nitrocumyl radical is ready to react with a high concentration of **2**$^-$ to give the cross coupling adduct radical anion **5**$^{-\bullet}$ It is also worth commenting that the synthetic method using the photostimulated $S_{RN}1$ mechanism of the P(O)-stabilized carbanion with the sterically hindered *p*-nitrobenzyl halides for the preparation of α-mono and α,α-disubstituted phosphonates can be easily employed when an Arbuzov C-P coupling reaction is difficult.

Experimental details are as follows: BuLi (2.4 mmol) was added to a solution of **2a** (2.4 mmol) in DMSO (10 mL) under argon atmosphere. The solution was stirred for 10 minutes before 2.4 mmol of *p*-nitrocumyl chloride **4a** in 2 mL of DMSO was slowly added by hypodermic syringe over a 2 minute period. The reaction mixture was irradiated by sunlamp for the time period described in Table 1. Addition of dilute HCl solution, followed by separation of the organic layer in conjunction with usual aqueous work up gave the crude mixture. After work-up, diiodomethane was added as an internal standard and the yield was measured by ^1H NMR integration. GLC response factors were also determined by *Least Squares* with four separate runs of authentic samples and internal standard.

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[#] Present address for correspondence to Jong Uk Rhee: Department of Chemistry, The Ohio State University, Columbus, OH 43210.

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