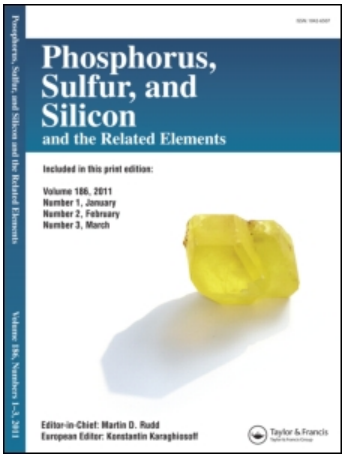

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Ding, Yixiang , Liu, Zhongfa , Zhou, Haiyan and Wang, Wenhui(1998) 'The Nucleophile-Catalyzed Atherton-Todd Reaction', Phosphorus, Sulfur, and Silicon and the Related Elements, 134: 1, 531 — 536
To link to this Article: DOI: 10.1080/10426509808545494
URL: http://dx.doi.org/10.1080/10426509808545494

Phosphorus, Sulfur and Silicon, 1998, Vol. 134/135, pp. 531-536
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THE NUCLEOPHILE-CATALYZED ATHERTON-TODD REACTION

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(Received 6 April, 1998; In final form 6 May, 1998)

Two examples of nucleophile catalyzed Atherton-Todd reaction was reported. In the presence of triethylamine α-sulfonyl group stabilized carbanions gave directly carbon-phosphorus compounds, e.g. 1-halo-1-arylsulfonylmethylphosphonate. The reaction of carbohydrates with thiophosphite was catalyzed by KI to give carbohydrate thiophosphates in good yield.

Keywords: Atherton-Todd reaction; nucleophilic catalysis; phosphonates; carbohydrate thiophosphates

Atherton-Todd reaction was used widely in phosphorylation of alcohols and amines[1]. The L-L PTC version of this reaction appears more convenient and versatile[2]. However the preparative usefulness of this procedure is also limited to primary alcohol and lower dialkyl phosphites as phosphorylating agents. Quite recently, several significant results of this reaction have been reported. Dialkyl thiophosphite[3] reacted with phenol, amines and other nucleophiles to give thiophosphoric acid derivatives. Silverberg[4] reported the selective phosphorylation of phenols. Our group[5]also reported the preparation of carbohydrate phosphates by the S-L PTC modified procedure in good yield. This reaction is also used in the synthesis of biodegradable and bioresorbable polymers containing phosphorus[6]. But the Atherton-Todd reactions of some nucleophiles are not satisfactory. To overcome these difficulties we would like to propose the application of nucleophilic catalysis in the Atherton-Todd reaction in this paper. Nucleophilic catalysis has been investigated in considerable detail owing to the importance of similar reactions in enzyme reactions. The imidazole-catalyzed alcoholysis of the diphosphate has been established[7a]. Toy[7b] also reported that certain tertiary amines catalyzed the reaction of diethyl chlorothiophosphate with

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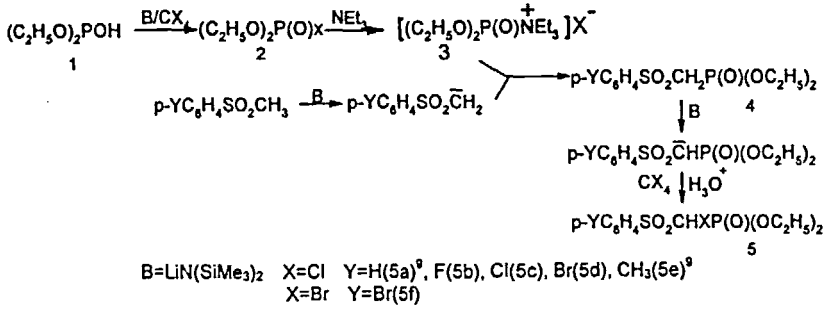
sodium phenolate. This technique has been used in the manufacture of insecticidal thiophosphates[7c] and in the studies of the stereochemistry[7d] of 2-substituted 1,3,2-oxazaphospholidin-2-ones. Recently, Hirschmann et al. have reported the first conclusive identification of a phosphonylammoniun salt as the intermediate of the triethylamine-catalyzed reaction of phosphonochloridate with nucleophiles[7e].

The reaction of carbanions with phosphoryl chloride has been developed as the important method[8] for the formation of carbon-phosphorus bonds. In the Atherton-Todd reaction diethyl phosphoryl chloride is an intermediate. The phosphorylation of carbanion by this method may be anticipated theoretically, but the formation of the carbon-phosphorus bond by this reaction has not been found in the literature so far. Now we find the successful phosphorylation of α-sulfonyl stabilized carbanion via nucleophile-catalyzed Atherton-Todd reaction by triethylamine and the direct synthesis of 1-halo-1-sulfonylmethylphosphonates as illustrated in the following equations.

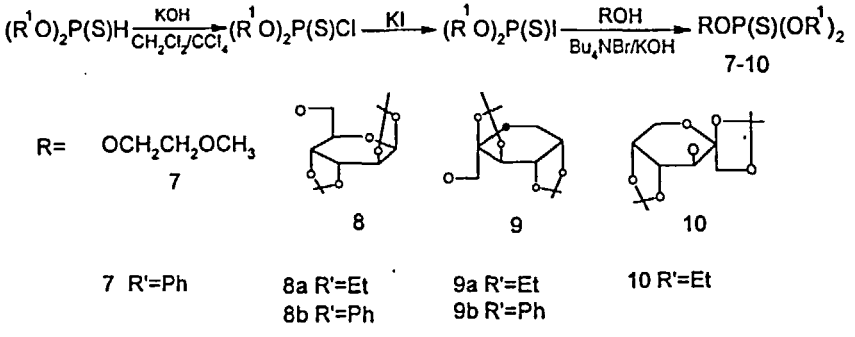


These reactions involved the transformation of phosphoryl chloride **2** formed in situ into the more active intermediate phosphorylammoniun salt **3** which underwent nucleophilic substitution on the phosphorus atom leading to the formation of phosphonates **4**. The latter existed as the corresponding carbanions and underwent the reaction with CCl_4 or CBr_4 to form substituted halomethylphosphonates **5**. So in this procedure it is necessary to use a three-fold excess of a strong base. Products **5** are important starting materials for the synthesis of substituted acetylenes. The alternative route may be that the carbanion derived from the sulfone was chlorinated first then reacted with **3** to form product **5**. If triethylamine was absent the reaction gave a very poor yield and formed some byproducts. The nucleophilic catalysis is often inhibited by steric hindrance, so $HN[SiMe_3]_2$ formed can not catalyze this reaction.

This result demonstrated the first example of formation of a carbon-phosphorus bond under Atherton-Todd condition and is a new method for the formation

of the carbon-phosphorus bond. The direct preparation of chloromethylphosphonates can be achieved in a one-pot procedure. The method is significantly much better than others described in literature[9]. It is noteworthy to point out that in Coutrot's[9] paper the lithium salt of aryl sulfonylmethylphosphonate can not be directly chlorinated with CCl_4.

The second successful example of nucleophile-catalyzed Atherton-Todd reaction is the preparation of the carbohydrate thiophosphates by using KI as catalyst. Although carbohydrate phosphates are easily prepared by S-L PTC Atherton -Todd reaction, the synthesis of the thiophosphates failed, because of the lower electrophilicity of the phosphorus atom in thiophosphoryl chloride. Using KI as a nucleophilic catalyst, the intermediate phosphoryl chloride was transformed into the more active phosphoryl iodide which then reacted with carbohydrate to give thiophosphates in good yield as shown below.



The novel procedure for the synthesis of carbohydrate thiophosphates has some advantages over other synthetic routes. The reaction is easy to operate and does not require anhydrous solvents. The use of an excess of phosphites favours the increase of yield. Both diethyl and diphenyl phosphite have the same reactivity. The carbohydrate thiophosphates are the most important analogs of natural carbohydrate phosphates and used widely in pharmaceuticals and as biochemical tools. The new procedure should find wide application.

In this paper we have demonstrated that nucleophilic catalysis is an effective method for these unactivated nucleophilic agents to be used in the Atherton-Todd reaction under usual condition.

Because of triethylamine as a base in general procedure of the Atherton-Todd reaction, the above experimental results proposed a problem: was the nucleophilic catalysis often present? Recently, some results on the Atherton-Todd reaction mechanism have been described[10], but they only answered the question

how the intermediate phosphoryl chloride was produced and did not explained the difference between the nucleophilic substitution reaction of phosphoryl chloride and the Atherton-Todd reaction. We believe that nucleophilic catalysis of triethlyamine may exist at least in some examples of unactivated nucleophiles.

EXPERIMENTAL

Microanalyses were performed on a Rapid CHN-O-S analyser. Mass spectra were run on a Finnigan-MATB430 spectrometer. ^{1}H and ^{31}P NMR spectra of carbohydrate derivative and ^{1}H NMR spectra of phosphonates were recorded on a AMX-300(300MHZ) instrument and FX-90Q in $CDCl_3$ with TMS as internal standard and 85% H_3PO_4 as external standard, respectively.

General procedure of: 5a~f: To a dry CH_2Cl_2(5ml) solution of 1 mmol sulfone(3) was added $(Me_3Si)_2NLi$(3ml 1M solution in THF) at –78°C. After 0.5h stirring, triethylamine(0.5ml) was added, then a solution of diethyl phosphite (1mmol in 2ml dry CCl_4) was introduced over 30min. The reaction mixture after being warmed to r.t. was allowed to stand overnight, then acidified with saturated NH_4Cl solution. After work-up the residue was chromatographed on a silica-gel column using ethyl acetate-petroleum ether as eluents to give pure products.

General procedure of 7~10: To a stirred mixture of carbohydrate derivative (1mmol),tetra-n-butylammonium bromide (0.2–0.5 mmol), powdered KOH (10mmol) and KI (0.5~1.0mmol) in a mixed solvent (10ml) of dichloromethane-tetrachloromethane (1:0.2) was slowly added the solution of diphenyl thiophosphite (1.1–2.0mmol) in dichloromethane (1ml) at 10–15°C. The progress of the reaction was monitored by TLC. After the reaction was completed, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel to afford pure carbohydrate thiophosphates.

5b: 45%, m.p.45–7 , ^{1}H NMR(CCl_4): δ= 1.32 (t, 6H), 4.17 (m, 4H), 4.79 (d, 1H, $^{2}J_{PH}$=12Hz), 7.13–7.90 (m,4H). Anal. for $C_{11}H_{15}ClFO_5PS$(344.72), Calc: C38.30; H4.35. Found: C 38.60; H4.23.

5c: 60%, oil, ^{1}H NMR(CCl_4): δ= 1.33 (t, 6H), 4.18 (m, 4H), 5.07 (d, 1H, $^{2}J_{PH}$=13.5Hz), 7.48–7.93 (m,4 H). Anal. for $C_{11}H_{15}Cl_2O_5PS$(361.17), Calc: C 36.56; H 4.15. Found: C 36.10; H: 3.77.

5d: 72%, oil, ^{1}H NMR(CCl_4): δ=1.40 (t, 6H), 4.27 (m, 4H), 4.98 (d, 1H,$^{2}J_{PH}$=12.6Hz), 7.70–7.90 (m,4H). Anal. for $C_{11}H_{15}BrClO_5PS$(405.62), Calc: C32.50; H 3.69. Found: C 32.11; H3.36.

5f: 80%, m.p.37–9, ^{1}H NMR(CCl_4): δ= 1.37 (t, 6H), 4.22 (m, 4H), 4.84 (d, 1H, $^2J_{PH}$=11.7Hz), 7.53–7.82(m,4H). Anal. for $C_{11}H_{15}Br_2O_5PS$(450.07), Calc: C29.27; H 3.54. Found: C 28.76; H3.74.

7: 62%, oil, ^{1}H NMR(CCl_4): δ= 3.44(s,3H), 3.70(t,2H), 4.41(m,2H), 7.3(m,10H). ^{31}P: δ 59.27. MS(m/z,%): 352(M+1,65.41), 293(7.52), 267(41.97), 94(51.74). Anal. for $C_{15}H_{17}O_4PS$(324.34), Calc: C55.54; H5.28; S9.88; Found: C55.24; H5.10; S10.09.

8a: 82%, oil, ^{1}H NMR($CDCl_3$): δ=1.22–1.50(m,18H), 4.25(dd,1H), 4.0–4.2(m,8H), 4.57(dd,1H), 5.43 (dd,1H). ^{31}P: δ=68.43. MS: m/z(%) = 413(M+1,12.86), 397(22.39), 339(15.88), 242(20.64), 227 (29.92), 184 (40.79), 169(100), 97(34.09), 43(46.99). Anal. for $C_{16}H_{29}O_8PS$(412.42), Calc: C46.59; H7.08; S7.78; Found: C46.33; H7.05; S8.03.

8b: 65%, oil, ^{1}H NMR($CDCl_3$): δ=1.25(s,6H), 1.45(s,3H), 1.48(s,3H), 4.16(t,1H), 4.24(dd,lH), 4.3~4.5 (m,3H), 4.63(dd,1H), 5.57(d,H), 7.2~7.4(m,10H). ^{31}P: δ=58.94. MS:m/z(%)=509 (M+!,32.19), 493(11.51), 451(11.74), 435(1023), 392(7.64), 342(30.32), 267(38.72), 227(44.03), 184(45.22), 169(100). Anal. For $C_{24}H_{29}O_8PS$(508.51), Calc: C56.69; H5.75; S6.31, found: C56.41; H6.02; S6.79.

9a: 75%,oil, ^{1}H NMR($CDCl_3$): δ=1.2~1.5(m,18H), 3.62(dd,1H), 3.79(dd,1H), 3.90(m,2H), 4.1(m,5H), 4.28(s,1H), 4.52(dd,1H). ^{31}P: δ= 67.87. MS: m/z(%)= 413(M+1,3.39), 397(40.92), 354(20.76), 279 (43.76), 185(40.49), 171(100), 141(42.94), 126(40.64), 97(44.87), 43(84.20). Anal. for $C_{16}H_{29}O_8PS$ (412.42), Calc: C46.59;H7.08; S7.78; S 7.78, found: C46.76; H7.23; S7.88.

9b: 83%, oil, ^{1}H NMR($CDCl_3$): δ=1.34, 1.36, 1.47, 1.55(sep. S,3H), 3.70(d,1H), 3.95(dd,1H), 4.22~4.47 (m,4H), 4.64(dd,1H), 7,15~7.4 (m,10H). ^{31}P: δ = 58.31. MS: m/z(%)= 509(M+1,15.83), 493(27.02), 451 (70.57), 375(43.41), 267(64.28), 185(74.03), 141(48.54), 124(59.35), 94(40.66), 43(100). Anal. For $C_{24}H_{29}O_8PS$(508.51), calc: C56.69; H5.75; S6.31; found: C56.33; H5.88; S6.89.

10: 74%, oil, ^{1}H NMR($CDCl_3$): δ = 1.32(m,6H), 1.35, 1.43, 1.54(sep. S,3H), 3.9~4.3(m,10H), 4.55 (dd,lH). ^{31}P: δ = 69.181. MS: m/z(%) = 413(M+1, 3.2), 355(9.81), 315(24.79), 279(14.39), 171 (100), 155 (64.58), 143(32.26), 127(41.30), 115 (28.07), 99(46.57). Anal. for $C_{16}H_{29}O_8PS$ (412.42), Calc: C46.59; H7.08; S7.78; found: C46.32; H7.32; S8.12.

The project was supported by the National Nature Science Foundation of China.

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