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McKenna Reaction—Which Oxygen Attacks Bromotrimethylsilane?

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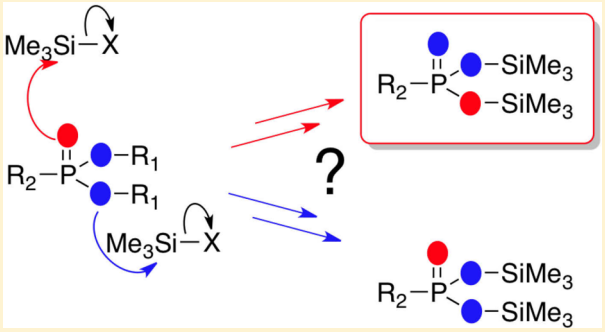
Supporting Information

ABSTRACT: The first experimental proof of the course of silylation in the McKenna reaction, one of the most widely used reactions for the synthesis of organophosphorus acids, is presented. The reaction (in acetonitrile) proceeds via an attack of the terminal oxygen from the dialkyl phosphonate on the silicon atom in bromotrimethylsilane. Isotopically enriched diethyl phenylphosphonates (P═^{17}O or P═^{18}O) were used as the model compounds. The location of the isotopic tracers was detected using ^{31}P and ^{17}O NMR spectroscopy.



The McKenna reaction[1,2] is one of the most widely used methods in the synthesis of organophosphorus acids. The application of commercially available bromotrimethylsilane (BTMS) ensures mild and efficient conditions for the transformation of pentavalent organophosphorus alkyl esters into trimethylsilyl esters, which are easily cleavable to free acids by the action of protic solvents.[2,3] Although it originally was applied only to dialkyl phosphonates, the method is also useful for dealkylation of phosphates and phosphinates. According to the Reaxys database,[4] BTMS and hydrochloric acid are the most often used reagents for dealkylation of organophosphorus esters. In the last two years (2012−2013), BTMS was used in at least half of such cases. Recent applications of other trimethylsilyl halides, chlorotrimethylsilane (CTMS)[5] and iodotrimethylsilane (ITMS),[6,7] for dealkylation of organophosphorus esters are less frequent.[8]

Two steps are involved in the BTMS-assisted synthesis of phosphonic acids (Schemes 1 and 2). In the first one, silyldealkylation takes place, converting dialkyl phosphonate ester **1** into bis(trimethylsilyl) phosphonate **5** (Scheme 2). In the second step, the silyl ester product **5** is subjected to solvolysis with the use of a protic solvent (Scheme 1).[9] The solvolysis step proceeds via nucleophilic attack on silicon by the oxygen atom of a protic solvent molecule, leaving a bridging oxygen from the ester in the molecule of the product acid **7** (Scheme 1). This was confirmed by Rabinowitz, who determined that the action of an alcohol on bis(trimethylsilyl) phosphonate resulted in the formation of a mixed ether, **8**.[5] Later on, Orlov and co-workers applied labeled water-^{18}O for solvolysis, and by using IR the authors detected isotopically labeled derivative **8** without formation of the labeled phosphonic acid.[10]

In contrast to the solvolysis step, the mechanism of the silylation is relatively unexamined. In their first report, in which BTMS silyldealkylation was carried out without added solvent, McKenna et al.[2] suggested that the terminal oxygen (P═O) attacks silicon, leading to phosphonium-like intermediates **2a** and **4a** (Scheme 2, mechanism A). Earlier, Rabinowitz had proposed this mechanism for CTMS-assisted dealkylation of dialkyl phosphonates.[5] Chojnowski, Michalski, and co-workers studied mechanistic aspects of the reaction of ITMS and BTMS with thio- and selenoesters of phosphorus.[7] However, in a recent kinetics study demonstrating that the BTMS reaction is second order, an alternate mechanism (Scheme 2, mechanism B) was postulated, involving nucleophilic attack on silicon by a bridging oxygen.[11]

In the mechanism proposed by McKenna (Scheme 2, mechanism A),[2] the terminal oxygen of compound **1** attacks the silicon atom, expelling bromide anion from BTMS and leading to the formation of a phosphonium-like intermediate **2a**. Next, P═O is recreated from one of the alkoxy groups upon attack of the bromide anion on the carbon neighboring a bridging oxygen, with formation of ethyl bromide. The new P═O then attacks another BTMS molecule to form **4a**, which upon an attack of bromide anion on the alkoxy carbon is transformed into bis(trimethylsilyl) phosphonate **5a**.

A proposed alternative mechanism (Scheme 2, mechanism B) involves the bridging oxygen of **1**, which attacks the silicon atom, resulting in the formation of intermediate **2b**. The bromide anion then attacks the carbon neighboring the positively charged oxygen in **2b**, forming ethyl bromide. The second alkoxy group (via **4b**) then undergoes an analogous transformation, and the final product **5b** is obtained.

Here, the first experimental proof of the mechanism of silylation in the McKenna reaction is presented. ^{31}P and ^{17}O NMR spectroscopy was used to determine which oxygen atom in the phosphonate moiety attacks silicon by following the fate of the labeled terminal oxygen (P═^{17}O and P═^{18}O). Readily available diethyl phenylphosphonate (**11**) was selected as a

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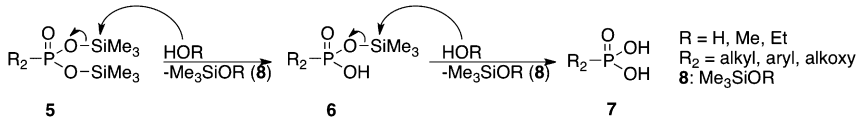
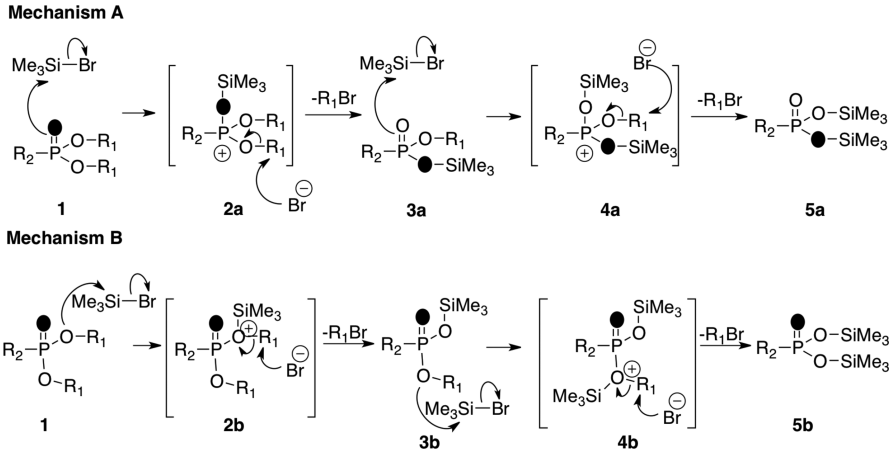
Scheme 1. Mechanism of Solvolysis of Bis(trimethylsilyl) Phosphonate



Scheme 2. Proposed Courses of the Silylation Reaction[a]

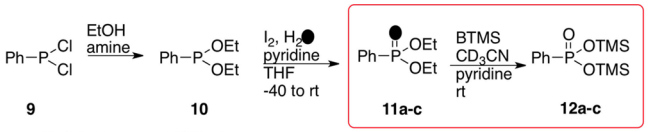


[a]The terminal oxygen is marked as a black oval to differentiate the two plausible mechanisms.

model compound, since it is a typical representative of phosphonates, the most abundantly studied class of organophosphorus esters. ^{17}O-enriched **11c** and its bis(trimethylsilyl) analogue **12c** have been fully characterized previously by ^{17}O NMR spectroscopy, with the chemical shifts of both the bridging and terminal oxygens being determined.[12] Such data make this ester an ideal reference compound for the studies presented here.

Diethyl phenylphosphonite (**10**) was prepared from dichloro(phenyl)phosphine (**9**).[13] Labeled and unlabeled diethyl phosphonates **11a–c** were prepared from **10** in the oxidation reaction with water and iodine.[14] This was a vital synthesis for these studies, since it enabled the introduction of an oxygen atom in the terminal P═O position.[15] Depending on the water used, phosphonates **11a–c** (Scheme 3) were obtained with high purity in 60–88% yield upon bulb-to-bulb distillation.

Scheme 3. Synthesis of Isotopically Labeled Substrate 11[a]



H_2● (>99 atom % ^{16}O): **11a**
H_2● (0.2 atom % ^{17}O, 98.6 atom % ^{18}O, 1.2 atom % ^{16}O): **11b**
H_2● (20.56 atom % ^{17}O, 15.65 atom % ^{18}O, 63.78 atom % ^{16}O): **11c**

[a]Silylation conditions are shown in the red rectangle. The labeled oxygen is marked as a black oval only for substrate **11**.

Silylation of the generated phosphonates **11** was carried out in an NMR tube in dry CD_3CN at room temperature. Spectra were recorded before and after addition of BTMS. The progress of the reaction was monitored by ^{31}P NMR spectroscopy. Exchange of one ethyl ester group for one trimethylsilyl residue shifts the phosphonate signal upfield by ~9 ppm, which is a characteristic marker for the progress of the McKenna reaction. To get good ^{31}P NMR resolution of the reaction mixture, the use of pyridine (as a proton scavenger) was necessary. Otherwise, an unresolved broad singlet in the ^{31}P NMR spectrum was observed (Figure S8 in the Supporting Information). This phenomenon might be associated with the presence of residual HBr in BTMS, leading to chemical exchange of a proton between the oxygen and proton donor.[16,17]

^{18}O is not magnetically active, but when it is directly linked with ^{31}P, it induces a small upfield shift in the ^{31}P NMR resonances[18,19] whose magnitude depends on, for example, the bond order.[20,21] The effect of isotopic substitution on the magnetic shielding of nuclei was predicted in 1952,[22] and since then it has been widely applied for studies of the mechanisms of a broad spectrum of chemical reactions.[20] Since in this case all of the oxygen atoms are directly connected to the ^{31}P nucleus, the bond order between phosphorus and oxygen was used as a probe, allowing determination of the reaction mechanism.

Depending on the reaction course, the phosphorus–oxygen bond order would change with P═O attack center (mechanism A) or would remain the same if the bridging oxygen were responsible for the attack on the silicon atom (mechanism B). It was reported that the difference between the chemical shifts of pentavalent phosphorus P═^{16}O and P═^{18}O should be in the range 0.043–0.052 ppm, whereas for P–^{16}O–R/P–^{18}O–R the difference should be smaller (0.016–0.032 ppm).[20]

In the first experiment, a mixture of diethyl ^{16}O-phosphonate ester **11a** and ^{18}O-phosphonate ester **11b** was monitored by ^{31}P NMR, giving a chemical shift difference of 0.045 ppm between **11a** and **11b** (Figure 1, on the left), corresponding to the value observed for analogous phosphonates labeled at the P═O oxygen.[20] Upon the action of BTMS, the chemical shift difference dropped to 0.028 ppm (Figure 1, on the right). This result confirms the phosphonium-like mechanism of the McKenna reaction, where the terminal oxygen attacks the silicon atom, changing the bond order from P═O to P–O–$SiMe_3$ (Scheme 2, mechanism A).

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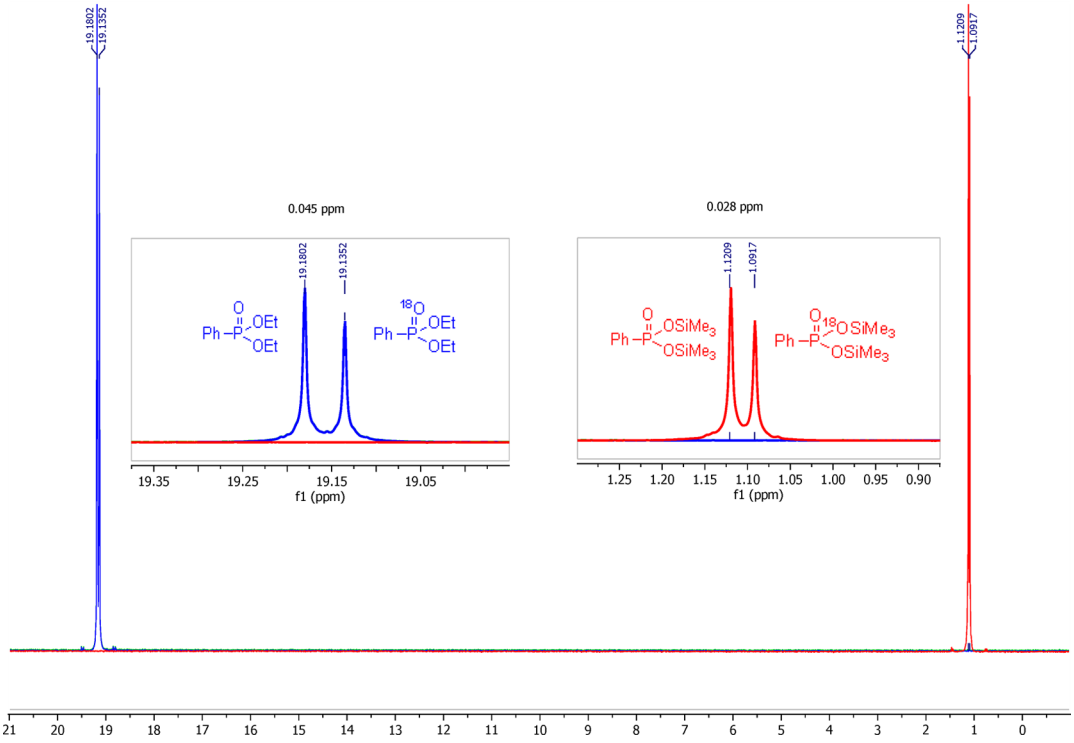

Figure 1. Superimposed ^{31}P NMR spectra of mixtures (molar ratio 1/0.8) of substrates **11a** and **11b** (blue, on the left) and products **12a** and **12b** (red, on the right).

Among the three naturally occurring oxygen isotopes, only ^{17}O possesses a nuclear spin ($I = {}^{5}/_{2}$). It is quadrupolar, which leads to rapid relaxation of the ^{31}P nucleus directly linked with ^{17}O and broadening of the line width.[20] Still, ^{17}O NMR analysis of P−O-containing compounds is appropriate for probing their structure, bonding, and dynamics[23] and is a valuable tool in some stereochemical analyses.[24] ^{17}O NMR spectroscopy allows differentiation between the terminal P═O and bridging P−O−R oxygens in organophosphorus derivatives[12] on the basis of their peak shapes (usually a well-resolved doublet for the P═O oxygen vs a broad peak for the P−O−R oxygen) or chemical shifts.[12] Application of ^{17}O NMR in titration studies showed that protonation of the phosphonate oxygen is accompanied by an upfield shift ∼50 ppm per charge neutralized.[25]

In the experiment with P═^{17}O-labeled phosphonate **11c**, ^{17}O NMR was used as the analytical tool. According to Dahn et al.,[12] in the case of phosphonate esters, substituting an alkyl group with a trimethylsilyl group shifts the signals of the terminal and bridging oxygens downfield by the same magnitude of 20−26 ppm. The chemical shifts for the terminal oxygen in **11c** and the bridging oxygen in bis(trimethylsilyl) ester **12c** were almost the same under the conditions applied.[12]

Here, upon addition of BTMS, the signal of oxygen originally present in P═^{17}O shifted downfield by only ∼4 ppm, suggesting that the phosphorus−oxygen bond order changed from P═O into P−O. This conclusion is strongly supported by the change in the peak shape from a well-resolved doublet for **11c** into a broad "singlet" for **12c** (Figure 2).

To sum up, the first experimental proof of the mechanism of the silylation in the McKenna reaction is presented. The results show that it is the P═O oxygen in diethyl phenylphosphonate that is responsible for the attack on the silicon atom in BTMS. Thanks to isotopic labeling of the terminal oxygen, the change in the phosphorus−oxygen bond order was directly observed

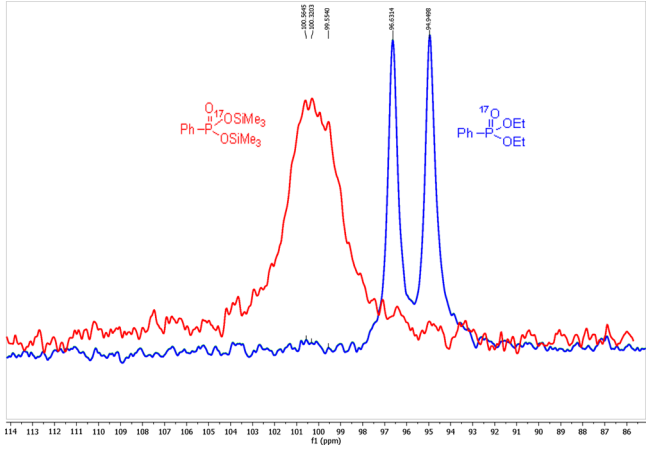

Figure 2. Superimposed ^{17}O NMR spectra of **11c** (in blue) and **12c** (in red).

by ^{31}P and ^{17}O NMR spectroscopies. The methodology presented here should be applicable to studies of other trimethylsilyl halogenides (CTMS and ITMS) as well as to other organophosphorus esters that are prone to BTMS-assisted dealkylation. It could be also useful to evaluate how different reaction conditions may influence the reaction mechanism.

EXPERIMENTAL DETAILS

Diethyl phenylphosphonite (**10**),[13] diethyl phenylphosphonate (**11**),[26] and bis(trimethylsilyl) phenylphosphonate (**12**)[27] were previously synthesized. Here compounds **11** were characterized by ^{31}P, ^{17}O, and ^{1}H NMR, and compounds **12** were characterized in the crude reaction mixture by ^{31}P, ^{1}H, and ^{17}O NMR. NMR spectra of substrates **11a−c** were acquired at 250.1 MHz for ^{1}H NMR and 101 MHz for ^{31}P NMR in $CDCl_3$, unless otherwise stated. NMR spectra of reaction mixtures

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before and after addition of BTMS were measured at 700.0 MHz for ^{1}H NMR, 283.4 MHz for ^{31}P NMR, and 94.9 MHz for ^{17}O NMR. Chemical shifts (δ) are reported in parts per million (ppm) relative to (a) in ^{1}H NMR, internal residual CH_3CN in CD_3CN (δ 1.96) or internal residual $CHCl_3$ in $CDCl_3$ (δ 7.26); in ^{31}P NMR, external 85% H_3PO_4 (0 ppm); and in ^{17}O NMR, external residual $D_2{}^{17}O$ in D_2O (0 ppm). Experiments were performed in NMR tubes, dried with the heat gun, and stored above P_2O_5 under vacuum. CD_3CN was dried with freshly activated 3 Å molecular sieves. Pyridine was distilled and dried with 3 Å molecular sieves. BTMS was distilled under nitrogen and stored in sealed ampules at −20 °C. Water-^{17}O (20−24.9 atom % ^{17}O) was acquired from Sigma-Aldrich and was also enriched with ^{18}O (20.56 atom % ^{17}O, 15.65 atom % ^{18}O, 63.78 atom % ^{16}O). Water-^{18}O (98%) was acquired from Sercon (0.2 atom % ^{17}O, 98.6 atom % ^{18}O, 1.2 atom % ^{16}O). The instrumental settings were as follows. For ^{17}O NMR: FIDRES, 0.072385 Hz; AQ, 6.9 s; D1, 2s; LB, 15 Hz. For determination of the ^{18}O isotopic shift in ^{31}P NMR: a spectral width of 11312.2 Hz and TD = 65536 gave high spectral resolution (FIDRES: 0.1726 Hz); AQ, 2.9 s; D1, 2 s; LB, 0.5 Hz. Compound **10** was prepared according to the reported procedure in 75% yield.[13]

Diethyl Phenylphosphonate (11). Diethyl phenylphosphonite (0.3 g, 1.51 mmol) was dissolved in THF (6 mL). After addition of pyridine (0.25 mL), the solution was cooled to −45 °C, and two liquids, appropriately labeled water (0.09 mL, 3 equiv)[28] and iodine (0.45 g, 1.77 mmol, 1.17 equiv) dissolved in THF, were added simultaneously via separate syringes until the yellow color persisted. After addition, the temperature was maintained at −45 to −35 °C for 10 min and then at rt for 10 min. The reaction was then quenched with a saturated solution of $Na_2S_2O_3$, and THF was evaporated. The residue was suspended in diethyl ether (50 mL), washed with 0.1 M HCl (5 × 1 mL) and water (3 × 1 mL), and then dried over $MgSO_4$. The resultant crude product was distilled bulb-to-bulb at 135 °C/0.1 mmHg. The final products were obtained in good yields (**11a**, 60%; **11b**, 83%; **11c**, 88%). ^{1}H NMR (250 MHz, $CDCl_3$, on the example of **11c**): δ 1.32 (t, $^{3}J_{HH}$ = 7.10 Hz, 2CH_3CH$_2$O, 6H); 3.99−4.23 (m, 2CH$_3$CH_2O, 4H); 7.42−7.59 (m, 3H$_{ar}$); 7.76−7.86 (m, 2H$_{ar}$). ^{31}P NMR (101 MHz, $CDCl_3$): δ 19.78. ^{17}O NMR (94.9 MHz, CD_3CN): δ 96.78 (d, $^{1}J_{OP}$ = 158.83).[26]

Bis(trimethylsilyl) Phenylphosphonate (12). The appropriately labeled diethyl phenylphosphonate (15 mg scale; 20% ^{17}O for ^{17}O NMR experiments or 45% ^{18}O for ^{31}P NMR experiment) was dissolved in dry acetonitrile-d_3 (0.6 mL), placed in an NMR tube, and subjected to the action of BTMS (5 equiv). After storage over the weekend at rt without stirring, NMR spectra were recorded and showed full conversion of the diethyl ester into the expected product **12**. NMR spectra were recorded for the crude reaction mixture. Below only signals confirming structure **12** are presented. For the spectra of reaction mixtures (with signals from additional compounds described), see Figures S13 and S19 in the Supporting Information. ^{1}H NMR (700 MHz, CD_3CN, on the example of **12c**): δ 0.43 (bs, 2Si(CH$_3$)$_3$, 18H);[27] 7.50−7.53 (m, 2H$_{ar}$); 7.59−7.61 (m, 1H$_{ar}$); 7.73−7.77 (m, 2H$_{ar}$). ^{31}P NMR (283.35 MHz, CD_3CN): δ 1.12 (**12a**);[27] 1.09 (**12b**); 1.12 and 1.09 in a 3.7:1 molar ratio (**12c**). ^{17}O NMR (94.91 MHz, CD_3CN): δ 100.8 (very broad singlet).

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{31}P NMR, ^{1}H NMR, and ^{17}O NMR spectra of diethyl phenylphosphonates **11** and crude reaction mixtures before and after addition of BTMS. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The author declares no competing financial interest.

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(8) ITMS is a more vigorous reagent than BTMS, often requiring lower temperatures of application (e.g., −20 °C) to avoid side reactions. In some cases (e.g., thiophosphonates) it successfully replaces BTMS in reactions with analogues requiring harsher conditions for dealkylation.[7]
(9) The ease of deprotection of bis(trimethylsilyl) phosphonates by solvolysis was shown earlier by Rabinowitz.[5] In their later works, McKenna and co-workers showed the importance of pH and buffering[29] and the possibility of controlled deprotection of other groups by the action of the deprotected phosphonic acid.[30]
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(17) The use of pyridine before addition of BTMS resulted in *N*-alkylation of pyridine with ethyl bromide, which forms upon the attack of bromide anion on phosphonium intermediates **2** and **4** (Scheme 2). This side reaction did not have any influence on the silylation reaction but could be avoided by adding the pyridine after the silylation was completed. According to the experience of the author and her co-workers, such *N*-alkylation is sometimes encountered when the McKenna reaction is applied to organophosphorus esters containing a heterobase residue. However, it can be easily circumvented by running the reaction in an atmosphere of flowing neutral gas, which removes the relatively volatile alkyl bromide from the reaction mixture.[31]
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