Beckmann Fragmentation and Successive Carbon–Carbon Bond Formation Using Grignard Reagents via Phosphonium Salt Intermediates

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The intermediates formed during the Beckmann fragmentation of \( \alpha \)-alkoxy and \( \alpha \)-alkoxy-\( \alpha \)-alkyl oxime acetates have been successfully trapped as phosphonium salts, which were subsequently reacted with a variety of Grignard reagents to give the corresponding substituted products in good yields. Notably, this reaction proceeded smoothly even from \( \alpha \)-alkoxy-\( \alpha \)-alkyl oxime acetates.

Key words Beckmann fragmentation; phosphonium salt intermediate; Grignard reagent; carbon–carbon bond formation

We recently found that the treatment of acetals with a combination of trifluoromethanesulfonic acid trialkylsilyl ester (R₃SiOTf) and base (e.g., pyridinium-type bases or triarylphosphines) gave the corresponding electrophilic pyridinium or phosphonium salts as stable intermediates. We subsequently showed that these salts can be used as stable synthetic equivalents of oxonium ions from acetals, and went on to develop a series of acetal substitution reactions using a variety of different nucleophiles (Eq. 1).¹⁻¹⁰ One of the main advantages of our new methods is that the nucleophiles can be added to the reaction mixture long after the formation of the intermediate salts. Furthermore, these methods are compatible with a wide variety of nucleophiles, including acid and base labile nucleophiles. It is noteworthy that acid labile nucleophiles cannot normally be used in the reactions of oxonium ions, because oxonium ions are usually formed under Lewis acidic conditions in the presence of a nucleophile, which would preclude the use of an acid labile nucleophile.¹¹ We subsequently investigated the application of this salt chemistry to another reaction involving sequential Beckmann fragmentation/carbon–carbon (C–C) bond forming reactions, which has been previously reported by our group using organoaluminum reagents.¹²⁻¹⁵ The treatment of \( \alpha \)-alkoxy oxime acetates with trifluoromethanesulfonic acid trimethylsilyl ester (TMSOTf) and 2,4,6-collidine produced the corresponding collidinium salt intermediates, which were successfully subjected to a C–C bond forming reaction with a variety of different Gilman reagents (Eq. 2).¹⁶ Gilman reagents were found to be the best type of organometallic carbon nucleophile for this reaction, with several other more popular organometallic reagents, including organolithium and Grignard reagents, failing to provide good results. However, we previously found that the phosphonium salts derived from \( O,O \)-acetals and (o-tol)₃P reacted smoothly with Grignard reagents.⁸⁻¹⁰ We therefore envisioned that the formation of a phosphonium salt instead of a collidinium salt would make it possible to use Grignard reagents in this reaction, which would represent a significant improvement over our previous method in terms of its scope and convenience.

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Results and Discussion

We initially investigated the generation of the phosphonium salt intermediate 2a from the model α-methoxy oxime acetate substrate 1a by 1H-NMR spectroscopy. Compound 1a is an E,Z-mixture and its stereochemistry was not determined. The spectra of 1a and the reaction mixture obtained by the treatment of 1a with TMSOTf (2 eq.) and (o-tol)3P (3 eq.) in CDCl3 are shown in Fig. 1. The appearance of a characteristic signal around 5.8 ppm suggested the formation of the O,P-acetal salt intermediate 2a.

Consequently, we investigated the optimum conditions for the transformation (Table 1). The treatment of 1a with TMSOTf (2 eq.) and (o-tol)3P (3 eq.) in CH2Cl2 at 0°C afforded the phosphonium salt 2a, which was detected by TLC as a polar spot. Several different organometallic reagents were then added to the reaction mixture. The addition of Ph2CuLi, PhMgBr or (PhMgBr)–CuI to the reaction mixture led to the formation of the desired product 3a (Table 1, Entries 1–3), whilst the addition of PhLi or Ph2Zn provided a complex mixture (Table 1, Entries 4, 5). When THF was used as the reaction solvent instead of CH2Cl2, we observed a slight decrease in the yield of 3a following the addition of Ph2CuLi, PhMgBr or (PhMgBr)–CuI (Table 1, Entries 6–8). Pleasingly, the Grignard reagent PhMgBr gave the best results in both solvents (Table 1, Entries 2, 7). Based on these results, CH2Cl2 was selected as the optimum solvent for the transformation, and the Grignard reagent was selected as the best carbon-based nucleophile.

With the optimized conditions in hand, we proceeded to investigate the scope of the reaction using a variety of differ-
ent oxime acetates and Grignard reagents (Table 2). Several Grignard reagents, including PhMgBr (Table 2, Entry 1), allylMgBr (Table 2, Entry 2) and MeMgBr (Table 2, Entries 3–8) reacted smoothly under these conditions. Various alkyl and silyl ethers, including methyl (Table 2, Entries 1–3), benzyl (Table 2, Entry 4), p-methoxybenzyl (PMB) (Table 2, Entry 5) and tert-butylmethylsilyl (TBS) ethers (Table 2, Entry 6) were also well tolerated. The eight- and twelve-membered ring oxime acetates 1e and f afforded the corresponding products 3g and h in high yields (Table 2, Entries 7, 8).

The advantage of using a phosphine in this reaction was demonstrated by the following experiments involving α-methyl-α-methoxy oxime acetate (4a), which has a tertiary alkoxide group (Chart 1). None of the desired pyridinium salt was formed by the treatment of 4a with TMSOTf and 2,4,6-collidine at 0°C (Table 3, Entry 1). We then conducted a detailed screening process to allow for the optimization of the reaction conditions. We initially examined the reaction temperature because of the poor stability of the intermediate. Unfortunately, tert-methoxycyanide 6a having quaternary carbon was obtained in 34% yield by following the addition of the Grignard reagent MeMgBr to the intermediate instead of H2O (Table 3, Entry 1). We then conducted a detailed screening process to allow for the optimization of the reaction conditions. We initially examined the reaction temperature (Table 3, Entries 1–3). The oxime substrate 4a disappeared completely and gave the desired product 6a in 84% yield when the reaction was conducted at −40°C (Table 3, Entry 2). These results indicated that the phosphonium salt intermediate generated from α-alkyl-α-methoxy oxime acetate was less stable than the intermediate generated from α-methoxy oxime acetate. Furthermore, although the phosphonium salt intermediate generated from the acetal (not the ketal) and PPh3 required a longer reaction time to undergo the substitution reaction (0°C, 96 h, 47%) in our previous work,8 the substitution reaction of the phosphonium salt from 4a reached completion in 2 h. However, the oxime substrate 4a was not completely consumed at −78°C (Table 3, Entry 3). It is noteworthy that only trace quantities of the desired product 6a were detected when the reaction was conducted in the absence of PPh3 (Table 3, Entry 4), which proved that the addition of a phosphine base was necessary for this reaction and that the reaction proceeded via a phosphonium salt intermediate.

The reactivities of two different phosphines (i.e., PPh3 and (o-tol)3P) were also examined in this reaction (Table 4). These two phosphines afforded the poor results. In the case of PPh3, substitution step maybe didn’t work well,17–19 whereas in the

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Table 3. Optimization of Reaction with α-Alkyl-α-methoxy Oxime Acetate

| Entry | Temp. | Yield |
|-------|-------|-------|
| 1     | 0°C   | 34%   |
| 2     | −40°C | 84%   |
| 3     | −78°C | 19%   |
| 4(+)  | −40°C | Trace |

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(a) Without PPh3.
case of (o-tol)₃P the formation of salt intermediate might be insufficient most likely because of its larger steric bulk (Table 4, Entries 2, 3 vs. Entry 1).

We subsequently examined a variety of oxime acetates and Grignard reagents (Table 5). α-Methyl (Table 5, Entries 1–3), α-allyl (Table 5, Entry 4) and α-phenyl (Table 5, Entry 5) oxime acetates reacted smoothly under the optimized conditions. Several Grignard reagents, including PhMgBr (Table 5, Entry 1), allylMgBr (Table 5, Entry 2) and MeMgBr (Table 5, Entries 3–5) also worked well under these conditions.

**Conclusion**

We have successfully trapped the intermediate formed during the Beckmann fragmentation reaction as a phosphonium salt and evaluated its reactivity towards a variety of different Grignard reagents in a C–C bond forming reaction. It is noteworthy that α-alkoxy-α-alkyl oxime acetates performed well as substrates for these reactions via the corresponding phosphonium salts, whereas the reactions via the corresponding collidinium salt intermediates were unsuccessful.

The application of this method to other reactions involving oxonium ions is currently under way in our laboratory.

**Experimental**

**General Information**

1H-NMR and 13C-NMR spectra were measured by JEOL JNM-GX 500, JEOL JNM-ECS 400 or JEOL JNM-AL 300 spectrometers with tetramethylsilane as an internal standard. IR spectra were recorded by Shimadzu FTIR 8400 using a diffuse reflectance measurement of samples dispersed in KBr powder. Column chromatography was performed with SiO₂ (Silicagel 60 (230–400 mesh or spherical, 63–210 μm).

**Compounds 1a–f, 3a, b and d–h Are Known Compounds**

General Procedure for the Synthesis of Oxime Acetate Substrates 1 or 4

Ketone (1 eq.) and NH₂OH·HCl (1.5 eq.), sodium acetate (1.65 eq.) were combined in MeOH (0.3 mol ketone) at room temperature under N₂ atmosphere. After the disappearance of starting material (judged by TLC analysis), H₂O was added to the reaction mixture. The resulting mixture was extracted by CH₂Cl₂. The organic layer was dried over Na₂SO₄, and concentrated in vacuo.

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**Typical Procedure for Beckmann Fragmentation and the Following C–C Bond Formation (Tables 1, 2) Synthesis of 3a**

TMSOTf (130 μL, 0.704 mmol) was added slowly to a solution of 1a (65.2 mg, 0.352 mmol) and (o-tol)₃P (320 mg, 1.05 mmol) in dry CH₂Cl₂ (3.5 mL, 0.1 mol) at −5°C under N₂ atmosphere. After the disappearance of 1a (judged by TLC analysis), PhMgBr (1.05 mmol) was added to the reaction mixture and the resulting mixture was warmed to room temperature. After 2 h, sat. aq. NH₄Cl was added to the reaction mixture. The resulting solution was extracted by CH₂Cl₂.

The organic layer was dried over Na₂SO₄, and concentrated in vacuo. The residue was purified by SiO₂ column chromatography (hexane–AcOEt = 1:1) to give 3a (50.8 mg, 71%) as yellow oil.

**6-Methoxyhexan-3-ene (3e)**

1H-NMR (CDCl₃, 500 MHz) δ: 1.14 (d, 3H, J=6.3 Hz), 1.41–1.58 (m, 4H), 1.65–1.71 (m, 2H), 2.36 (t, 2H, J=7.2 Hz), 3.28–3.33 (m, 1H), 3.32 (s, 3H). 13C-NMR (CDCl₃, 125 MHz) δ: 17.1, 18.8, 24.6, 25.4, 35.5, 56.0, 76.3, 119.7. IR (KBr cm⁻¹): 2247. MALDI-TOF-MS m/z: 164.1046 (Calcd for C₇H₁₄NONa [M+Na⁺] : 164.1046).

1-Cyano-5-oxohexane (5)

1H-NMR (CDCl₃, 300 MHz) δ: 1.59–1.77 (m, 4H), 2.16 (s, 3H), 2.36 (t, 2H, J=6.7 Hz), 2.51 (t, 2H, J=6.7 Hz). 13C-NMR (CDCl₃, 125 MHz) δ: 16.9, 22.5, 24.7, 29.8, 42.2, 51.9, 104.7. IR (KBr cm⁻¹): 1713, 2246. MALDI-TOF-MS m/z: 148.0732 (Calcd for C₅H₉NO [M+[Na⁺] : 148.0732).

**Typical Procedure for Beckmann Fragmentation and the Following C–C Bond Formation (Tables 4, 5) Synthesis of 6a**

TMSOTf (83 μL, 0.460 mmol) was added slowly to a solution of 4a (45.8 mg, 0.230 mmol) and PPh₃ (180 mg, 0.690 mmol) in dry CH₂Cl₂ (2.3 mL, 0.1 mol) at −40°C under N₂ atmosphere. After the disappearance of 4a (judged by TLC analysis), MeMgBr (0.690 mmol) was added to the reaction mixture and the resulting solution was warmed to room temperature. After 2h, sat. aq. NH₄Cl was added to the reaction mixture. The mixture was extracted by CH₂Cl₂.

The organic
layer was dried over Na$_2$SO$_4$, and concentrated in vacuo. The residue was purified by SiO$_2$ column chromatography (hexane–AcOEt=5:1) to give 6a (30.0 mg, 84%) as yellow oil.

6-Methoxy-6-methylheptanenitrile (6a)

$^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$: 1.15 (s, 6H), 1.47–1.58 (m, 4H), 1.65–1.69 (m, 2H), 2.36 (t, 2H, $J$=7.2 Hz), 3.18 (s, 3H).

$^{13}$C-NMR (CDCl$_3$, 125 MHz) $\delta$: 17.1, 39.1, 50.3, 74.2, 119.6, 144.7. IR (KBr) cm$^{-1}$: 2247. MALDI-TOF-MS m/z: 178.1198 (Calcd for C$_9$H$_{17}$ONa $^+$: 178.1202).

6-Methoxy-6-phenylheptanenitrile (6b)

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$: 1.22–1.32 (m, 2H), 1.56–1.62 (m, 2H), 1.73–1.77 (m, 2H), 2.27 (t, 2H, $J$=6.8 Hz), 3.09 (s, 3H), 7.34–7.39 (m, 5H). $^{13}$C-NMR (CDCl$_3$, 125 MHz) $\delta$: 17.0, 22.6, 23.2, 26.1, 42.4, 50.3, 78.7, 119.6, 126.0, 126.9, 128.2, 144.7. IR (KBr) cm$^{-1}$: 2252. High resolution (HR)-FAB-MS m/z: 217.1451 (Calcd for C$_{14}$H$_{19}$NONa $^+$: 217.1450).

6-Methoxy-6-methyl-8-nonenenitrile (6c)

$^1$H-NMR (CDCl$_3$, 400 MHz) $\delta$: 1.17–1.19 (m, 1H), 1.19 (s, 3H), 1.48–1.62 (m, 5H), 2.28 (t, 2H, $J$=7.1 Hz), 4.34 (s, 2H), 7.17–7.27 (m, 5H). $^{13}$C-NMR (CDCl$_3$, 125 MHz) $\delta$: 17.2, 23.2, 25.4, 25.9, 40.0, 63.7, 74.8, 119.8, 127.15, 127.24, 128.3, 139.6. IR (KBr) cm$^{-1}$: 2253. HR-FAB-MS m/z: 231.1615 (Calcd for C$_{15}$H$_{21}$NO $^+$: 231.1632).

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Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials ($^1$H-, $^{13}$C- and $^{19}$F-NMR charts of the reaction mixture of 2a, obtained by treatment of 1a with TMSOTf and P(o-tol)$_3$; $^1$H- and $^{13}$C-NMR charts of TMSOAc).

References and Notes

1) Fujioka H., Sawama Y., Murata N., Okitsu T., Kubo O., Matsuda S., Kita Y., J. Am. Chem. Soc., 126, 11800–11801 (2004).
2) Fujioka H., Okitsu T., Sawama Y., Murata N., Li R., Kita Y., J. Am. Chem. Soc., 128, 5930–5938 (2006).
3) Fujioka H., Okitsu T., Ohnaka T., Li R., Kubo O., Okamoto K., Sawama Y., Kita Y., J. Org. Chem., 72, 7898–7902 (2007).
4) Fujioka H., Minamitsuji Y., Kubo O., Senami K., Maegawa T., Tetrahedron, 67, 2949–2960 (2011).
5) Fujioka H., Okitsu T., Sawama Y., Ohnaka T., Kita Y., Synlett, 2006, 3073–3080 (2006).
6) Fujioka H., Yahata K., Hamada T., Kubo O., Okitsu T., Sawama Y., Ohnaka T., Maegawa T., Kita Y., Chem. Asian J., 7, 367–373 (2012).
7) Minamitsuji Y., Kawaguchi A., Kubo O., Ueyama Y., Maegawa T., Fujioka H., Adv. Synth. Catal., 354, 1861–1866 (2012).
8) Fujioka H., Goto A., Otake K., Kubo O., Yahata K., Sawama Y., Maegawa T., Chem. Commun., 46, 3976–3978 (2010).
9) Goto A., Otake K., Kubo O., Sawama Y., Maegawa T., Fujioka H., Chem. Eur. J., 18, 11423–11432 (2012).
10) Fujioka H., Goto A., Otake K., Kubo O., Sawama Y., Maegawa T., Chem. Commun., 47, 9894–9896 (2011).
11) Mukaiyama H., Murakami K., Synthesis, 1987, 1043–1054 (1987).
12) We reported Beckmann fragmentation of α-alkoxy oxime esters and the following introduction of nucleophile using Lewis acid–organosilicon reagent or organoaluminim reagent. See refs. 13–15.
13) Fujioka H., Miyazaki M., Yamanaka T., Yamamoto H., Kita Y., Tetrahedron Lett., 31, 9591–9594 (1990).
14) Fujioka H., Yamamoto H., Miyazaki M., Yamanaka T., Takuma K., Kita Y., Tetrahedron Lett., 32, 5367–5368 (1991).
15) Fujioka H., Yamanaka T., Takuma K., Miyazaki M., Kita Y., J. Chem. Soc., Chem. Commun., 1991, 533–534 (1991).
16) Fujioka H., Matsumoto N., Ohita R., Yamakawa M., Shimizu N., Kimura T., Murai K., Tetrahedron Lett., 56, 2656–2658 (2015).
17) Steric bulk of trialkylphosphine is much smaller than that of triarylphosphine. We also reported that the nucleophilic ability of trialkylphosphine is much stronger than that of triarylphosphine. See refs. 18 and 19.
18) Fujioka H., Yahata K., Kubo O., Sawama Y., Hamada T., Maegawa T., Angew. Chem. Int. Ed., 50, 12232–12235 (2011).
19) Yahata K., Minami N., Yoshikawa Y., Watanabe K., Fujioka H., Chem. Pharm. Bull., 61, 1298–1307 (2013).