Grignard-Triggered Fragmentation of Vinylogous Acyl Triflates: Synthesis of (*Z*)-6-Heneicosen-11-one, the Douglas Fir Tussock Moth Sex Pheromone

David M. Jones, Shin Kamijo, Gregory B. Dudley*

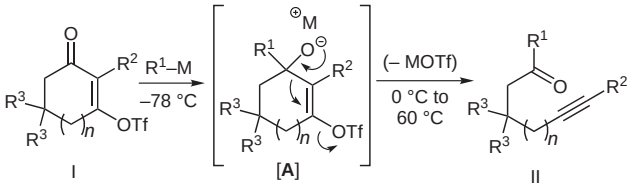
Department of Chemistry and Biochemistry, Florida State University, Tallahassee, FL 32306-4390, USA
Fax +1(850)6448281; E-mail: gdudley@chem.fsu.edu

Received 13 December 2005

Abstract: Grignard reagents react with vinylogous acyl triflates in toluene via an addition–fragmentation sequence to afford alkynyl ketones. A streamlined synthesis of (*Z*)-6-heneicosen-11-one, the sex pheromone of the Douglas fir tussock moth, illustrates the utility of this method.

Key words: synthesis, fragmentation, Douglas fir tussock moth

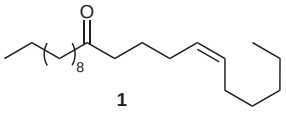
We recently disclosed preliminary findings from a carbanion-triggered addition–fragmentation methodology that we are pursuing in our laboratory.[1] Unstabilized carbon nucleophiles add to vinylogous acyl triflates **I** to generate [**A**], a tetrahedral intermediate with a vinylogous nucleofuge. Intermediate [**A**] then fragments by a Grob-type pathway[2] to afford a tethered keto alkyne (**II**, Scheme 1).[3] Nucleophilic addition (**I** → **A**) is faster than fragmentation (**A** → **II**), so overaddition does not occur; R^1–M is generally consumed prior to the formation of ketone **II**. Viable carbon nucleophiles for this reaction include organolithium reagents, lithium enolates, and aryl Grignard reagents.[1]



Scheme 1 Addition–fragmentation of vinylogous acyl triflates

We now report our efforts to apply this method to an efficient synthesis of (*Z*)-6-heneicosen-11-one (**1**), the sex attractant of the Douglas fir tussock moth.[4] Insect pheromones are of general interest as environmentally benign pesticide alternatives.[5] Such compounds are already part of the ecosystem; through controlled release of synthetic pheromones, one can disrupt the mating behavior of the pest. Pheromone **1** (Figure 1) in particular has attracted significant synthetic attention.[6]

The impetus for this endeavor derives from the fact that alkyl Grignard nucleophiles were beyond the scope of our initial reports. Grignard reagents are sometimes more



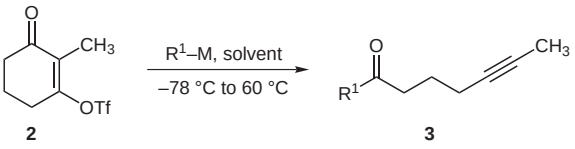
1

Figure 1 (*Z*)-6-Heneicosen-11-one (**1**)

accessible than the corresponding organolithiums. For example, *n*-decylmagnesium chloride, which would be needed for the synthesis of **1** by our method, is commercially available, whereas *n*-decyllithium is not. We therefore set out to optimize the reaction between triflate **2** and Grignard nucleophiles (Table 1).

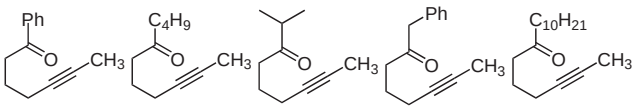
Aryl Grignard nucleophiles (e.g., entry 1) trigger fragmentation under our original conditions;[1] however, alkyl Grignards were not competent partners (entry 2).

Table 1 Grignard-Triggered Fragmentation of **2**[a]



2 **3**

Entry	R^1–M	Solvent[b]	Product	Yield (%)
1	PhMgBr	THF	**3a**	80
2	*n*-BuMgCl	THF	**3b**	–[c]
3	*n*-BuMgCl	Et_2O	**3b**	24[d]
4	*n*-BuMgCl	Toluene	**3b**	63–83
5	*i*-PrMgCl	Toluene	**3c**	–[c]
6	BnMgBr	Toluene	**3d**	73
7	*n*-DecylMgCl	Toluene	**3e**	58
8	PhMgBr	Toluene	**3a**	71



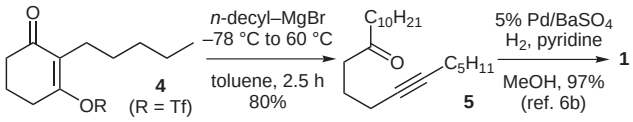
3a **3b** **3c** **3d** **3e**

[a] Solution of triflate **2** (1.1 equiv) treated with 1.0 equiv of R^1–M (in Et_2O) at –78 °C, warmed to r.t., and then heated at 60 °C for 30 min.
[b] Note that Et_2O is present in each case.
[c] Product was not obtained in acceptable purity.
[d] Reaction mixture was heated for 1 h at reflux (ca. 40 °C); fragmentation was incomplete.

SYNLETT 2006, No. 6, pp 0936–0938
Advanced online publication: 14.03.2006
DOI: 10.1055/s-2006-939051; Art ID: S12405ST

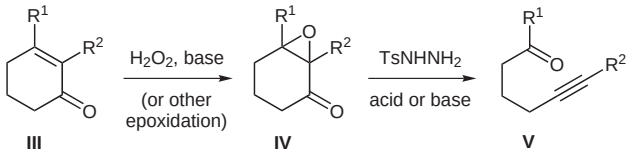
Toluene is the preferred solvent for the use of alkyl Grignard reagents in our addition–fragmentation method. Entries 2–4 are representative of our solvent screening process; the reaction of triflate **2** in toluene with an ethereal solution of *n*-butylmagnesium chloride afforded good yields of alkynyl ketone **3b** (entry 4). Benzylmagnesium bromide also reacted smoothly (entry 6), but branched alkyl Grignard reagents (e.g., isopropylmagnesium chloride, entry 5) were significantly less efficient in this process. The *n*-decyl nucleophile relevant to the synthesis of **1** provided an acceptable yield of ketone **3e** (entry 7). We reexamined phenylmagnesium bromide (entry 8), finding a modest and perhaps insignificant decrease in efficiency as compared to our previous report (entry 1).

We next turned our attention to the synthesis of **1** (Scheme 2). Vinylogous acyl triflate **4**[7] was treated with *n*-decylmagnesium bromide to afford keto alkyne **5** in one step.[8] Hydrogenation of alkyne **5** provides the moth pheromone **1**.[6b,9] Characterization data for our synthetic sample[10] is in accord with literature reports.[6]



Scheme 2 Synthesis of (*Z*)-6-heneicosen-11-one (**1**)

This anion-triggered C–C bond cleavage calls to mind the Eschenmoser–Tanabe reaction sequence, one of the classic fragmentation protocols and a valuable tool for preparing alkynyl ketones (Scheme 3).[11] Vinylogous acyl triflates provide more direct access to a similar pathway. For example, a vinylogous methyl ester (**4**, R = Me) was advanced to **1** in a four-step process that featured the Eschenmoser–Tanabe reaction (**4** → **III** → **IV** → **V** → **1**, R^1 = decyl, R^2 = pentyl).[6b] By enhancing the nucleofugacity of vinylogous ester **4** (Scheme 2, R = Tf vs. Me), one gains immediate access to the fragmentation product, streamlining the synthetic sequence.



Scheme 3 Eschenmoser–Tanabe fragmentation

In summary, we have extended the scope of our anion-triggered C–C bond cleavage reaction to include alkyl Grignard nucleophiles, and we applied our findings to the chemical synthesis of (*Z*)-6-heneicosen-11-one (**1**), the sex attractant of the Douglas fir tussock moth. Within the context of this study, toluene proved to be a significantly more effective solvent than THF. We are continuing to develop this method, and further applications will be reported in due course.

Acknowledgment

This research was supported by a grant from the James and Ester King Biomedical Research Program, Florida Department of Health, an award from Research Corporation, and by the FSU Department of Chemistry and Biochemistry. S.K. acknowledges the Japan Society for the Promotion of Science (JSPS) for the Postdoctoral Fellowship for Research Abroad (2004). We thank all of these agencies for their support. We thank Dr. Joseph Vaughn for assistance with the NMR facilities and Dr. Umesh Goli for providing the mass spectrometry data.

References and Notes

(1) (a) Kamijo, S.; Dudley, G. B. *J. Am. Chem. Soc.* **2005**, *127*, 5028. (b) Kamijo, S.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 175; a full account of this work, which includes a wider range of nucleophiles, is in preparation.

(2) (a) Grob, C. A.; Schiess, P. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1. (b) Grob, C. A. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 535. (c) Wharton, P. S.; Hiegel, G. A. *J. Org. Chem.* **1965**, *30*, 3254. (d) Weyerstahl, P.; Marschall, H. In *Comprehensive Organic Synthesis*, Vol. 6; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**, 1041.

(3) Analogues of [**A**] in which the triflate is replaced by a halide fragment under flash vacuum pyrolysis conditions: Coke, J. L.; Williams, H. J.; Natarajan, S. *J. Org. Chem.* **1977**, *42*, 2380.

(4) Smith, R. G.; Daterman, G. E.; Daves, G. D. Jr. *Science* **1975**, *188*, 63.

(5) (a) Hulme, M.; Gray, T. *Environ. Entomol.* **1994**, *23*, 1097. (b) Welter, S. C.; Pickel, C.; Millar, J.; Cave, F.; Van Steenwyk, R. A.; Dunley, J. *Calif. Agric.* **2005**, *59*, 17.

(6) There are more than thirty previous syntheses of **1**. Selected examples and leading references: (a) Smith, R. G.; Daves, G. D. Jr.; Daterman, G. E. *J. Org. Chem.* **1975**, *40*, 1593. (b) Kocienski, P. J.; Cernigliaro, G. J. *J. Org. Chem.* **1976**, *41*, 2927. (c) Mori, K.; Uchida, M.; Matsui, M. *Tetrahedron* **1977**, *33*, 385. (d) Fetizon, M.; Lazare, C. *J. Chem. Soc., Perkin Trans. 1* **1977**, 842. (e) Akermark, B.; Ljungqvist, A. *J. Org. Chem.* **1978**, *43*, 4387. (f) Trost, B. M.; Ornstein, P. L. *Tetrahedron Lett.* **1981**, *22*, 3463. (g) Murata, Y.; Inomata, K.; Kinoshita, H.; Kotake, H. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2539. (h) Reddy, G. B.; Mitra, R. B. *Synth. Commun.* **1983**, *16*, 1723. (i) Pramod, K.; Ramanathan, H.; Subba Rao, G. S. R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 7. (j) Sodeoka, M.; Shibasaki, M. *J. J. Org. Chem.* **1985**, *50*, 1147. (k) Wenkert, E.; Ferreira, V. F.; Michelotti, E. L.; Tingoli, M. *J. Org. Chem.* **1985**, *50*, 719. (l) Ballini, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1419. (m) Stowell, J. C.; Polito, M. A. *J. Org. Chem.* **1992**, *57*, 4560. (n) White, J.; Whiteley, C. G. *Synthesis* **1993**, 1141. (o) Hayes, J. F.; Shipman, M.; Twin, H. *J. Org. Chem.* **2002**, *67*, 935.

(7) Acyl triflate **4** (R = Tf) was prepared from 2-pentyl-1,3-cyclohexanedione[12] using triflic anhydride and pyridine by analogy to our published procedure, see. ref. 1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.75 (t, *J* = 6.2 Hz, 2 H), 2.47 (t, *J* = 6.8 Hz, 2 H), 2.32 (t, *J* = 7.6 Hz, 2 H), 2.07 (app quint, *J* = 6.5 Hz, 2 H), 1.22–1.42 (m, 6 H), 0.88 (t, *J* = 6.8 Hz, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.3, 161.7, 132.3, 36.9, 31.7, 28.64, 28.65, 28.0, 23.7, 22.2, 20.6, 13.8. HRMS (CI^+): *m/z* calcd for $C_{12}H_{18}O_4SF_3$: 315.0878; found: 315.0893.

(8) **Synthesis of Alkynyl Ketone (5)**
To a stirred solution of vinylogous acyl triflate **4**[7] (100 mg, 0.32 mmol) in toluene (3 mL) at –78 °C was added *n*-decylmagnesium bromide (0.31 mL, 0.93 M in Et_2O, 0.29 mmol). The reaction mixture was warmed to r.t. over 1 h, heated at

60 °C for 1.5 h, cooled to r.t., quenched with half-sat. NH_4Cl solution (10 mL), and extracted with Et_2O. The combined organic phases were washed with H_2O, dried ($MgSO_4$), concentrated, and purified on silica gel (elution with 1% EtOAc–hexanes) to afford alkynyl ketone **5** as an oil that solidified on standing; yield 70 mg (80%). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.52 (t, *J* = 7.3 Hz, 2 H), 2.40 (t, *J* = 7.5 Hz, 2 H), 2.08–2.23 (m, 4 H), 1.74 (app quint, *J* = 7.0 Hz, 2 H), 1.43–1.64 (m, 4 H), 1.19–1.38 (m, 18 H), 0.83–0.95 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 210.9, 81.1, 79.1, 43.0, 41.3, 31.9, 31.1, 29.6, 29.5, 29.4, 29.3, 28.8, 23.9, 23.0, 22.6, 22.2, 18.7, 18.2, 14.1, 13.1. HRMS (CI^+): *m/z* calcd for $C_{21}H_{39}O$: 307.3001; found: 307.2999.

(9) The $Pd/BaSO_4$ and pyridine must be mixed before adding alkyne **5** for best results.

(10) ^1H NMR (500 MHz, $CDCl_3$): δ = 5.37–5.41 (m, 2 H), 2.35–2.41 (m, 4 H), 1.94–2.06 (m, 4 H), 1.63 (app quint, *J* =7.4 Hz, 2 H), 1.21–1.37 (m, 22 H), 0.85–0.90 (m, 6 H). HRMS (CI^+): *m/z* calcd for $C_{21}H_{41}O$: 309.3157; found: 309.3158.

(11) (a) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, *50*, 708. (b) Felix, D.; Shreiber, J.; Ohloff, G.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 2896. (c) Tanabe, M.; Crowe, D. F.; Dehn, R. L. *Tetrahedron Lett.* **1967**, 3943. (d) Tanabe, M.; Crowe, D. F.; Dehn, R. L.; Detre, G. *Tetrahedron Lett.* **1967**, 3739.

(12) (a) Rosenmund, K. W.; Bach, H. *Chem. Ber.* **1961**, *94*, 2394. (b) Piers, E.; Grierson, J. R. *J. Org. Chem.* **1977**, *42*, 3755.