A Convenient Synthesis of 4-Ethyl-4-methyl-3-oxohexanenitrile via Pinacol Rearrangement

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A readily available source of 4-ethyl-4-methyl-3-oxohexanenitrile (1) was recently required for the synthesis of Isoxaben (2), a preemergent herbicide for cereal crops with additional utility in turf and ornamental application. On the basis of economic considerations, we sought to prepare 1 from commercially available starting materials in a straightforward fashion. The formation of ketone 7 by pinacol rearrangement of the symmetrical diol 3 was envisioned. Elaboration of 7 would then afford the title compound 1. This note outlines the realization of these goals, taking advantage of rather subtle reaction selectivities.

Bimolecular reductive coupling of methyl ethyl ketone (4) afforded the diol 3 utilizing a variety of reagents (Scheme I).[1] The coupling of 4 was first reported in 1922 with magnesium amalgam.[1a] Implementation of the Corey $TiCl_4$–Mg(Hg)[1b] protocol produced the desired diol 3 in 87% yield after distillation. SmI_2 could likewise be used to effect the identical coupling in excellent yield.[1c] Reaction with metallic sodium[1d] or photochemically[1e] induced dimerization afforded only trace amounts of product, which might be expected for enolizable ketones.[1e] Since the electrodimerization[1f] of acetone to pinacol has been well studied, this tactic appeared to be an attractive and inexpensive approach to obtain diol 3. However, with a variety of cathodes, electrolytes, and solvents, the selectivity for dimerization versus simple reduction (*sec*-BuOH production) and chemical efficiency were typically very low. Alternatives to the reductive dimerization included the condensation of 3,4-hexanedione (5) with 2 equiv of MeMgBr, or 2,3-butanedione (6) with EtMgBr in THF solution in 90% yield. Finally, the Zn/$TiCl_4$ protocol developed by Mukaiyama[1g] was also employed to produce the best overall yield (99%) of diol 3 with minimal byproducts, olefins or *sec*-BuOH.

Various aspects of the pinacol rearrangement have recently been discussed,[2] including the migratory aptitude of ethyl versus methyl.[3] Initially it was expected that the slight migratory preference for Et over Me might not afford practically useful levels of the desired ketone 7, although the first reported studies by Nybergh in 1922 established the 4:1 ratio of 7/8 (no yield reported). Nybergh also showed that $Et_2C(OH)C(OH)Me_2$ produced the same ketones 7/8 in a ratio of 1:20, further demonstrating the ethyl migratory preference. Kinetic studies by Stiles and Mayer[3c] proved the relative rates for pinacol rearrangements were 1:4.7:54 for $R_{migrating}$ = Me, Et, *t*-Bu, respectively. A recent computational study[4] on the migratory aptitude using *ab initio* SCF MO methods concluded that vinyl migration would be further enhanced *vis à vis* Me or H migration. This intriguing alternative, involving the dimerization of methyl vinyl ketone, was not reduced to practice, however. We optimized the Nybergh conditions as a function of H_2SO_4 (12 mole equiv), temperature (−40 → −10 °C) and time (2 h) to afford the ketones 7 and 8 (>90% yield, 4:1 ratio). Alternative acids were surveyed and are shown in Table I, although none provided any better product profile or efficiency than H_2SO_4. Therefore, H_2SO_4 was utilized for routine preparation of the key ketone intermediate.

Scheme I

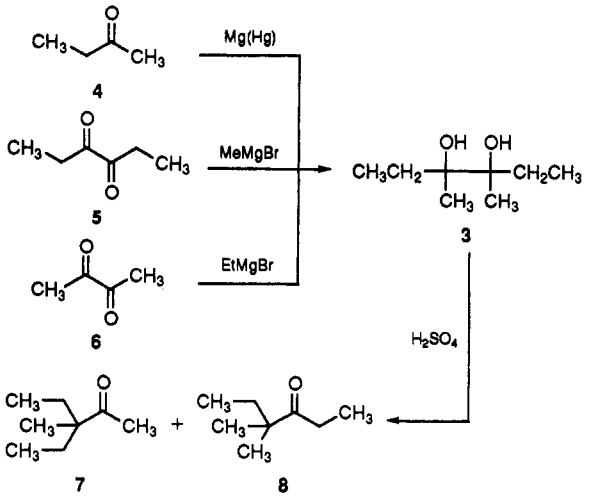

Table I. Alternative Acids for the Pinacol Rearrangement of 3 → 7 + 8

reaction medium	temperature, °C	time	7/8 ratio (% yield)
H_2SO_4 (12 equiv)	−40 → −10	2 h	4:1 (90)
H_2SO_4 (5 equiv)	−40 → 60	45 min	3.7:1 (57)
H_2SO_4 (1 equiv)	0 → 60	30 min	3.7:1 (98)
PPA (6 equiv)	20	1 h	2.7:1 (61)
HCO_2H (1 equiv)	5 → ambient	3 h	no reaction
TFA (1 equiv)	0 → ambient	18 h	no reaction
BF_3·Et_2O/CH_2Cl_2	0 → 55	40 min	2.4:1 (98)
H_3PO_4 (75%)	ambient	30 min	1.8:1 (55)
FSO_3H	0	30 min	2.7:1 (59)
p-TsOH (1 equiv)/ toluene	reflux	40 min	trace
HCl (concd, 12 equiv)	−5	15 min	4:1 (<50)

Addition of Br_2 to a mixture of ketones 7 and 8 in MeOH solution at 10 °C afforded selective bromination of the methyl ketone (Scheme II). Bromination of 8 occurred at warmer reaction temperatures to form α-bromoethyl ketone 10. To capitalize on this observation, titration of the ketone mixture 7/8 (4:1 ratio) with 0.8 equiv of bromine afforded a mixture containing uniquely the α-bromomethyl ketone 9 (67%) alongside unreacted ethyl ketone 8. To a first approximation, bromination of ketones has been shown to be first order in substrate, with enolization being

(1) (a) Nybergh, B. *Chem. Ber.* **1922**, *55B*, 1960. (b) Corey, E. J.; Danheiser, R. L.; Chandrasekaran, S. *J. Org. Chem.* **1976**, *41*, 260. (c) Souppe, J.; Danon, L.; Namy, J. L.; Kagan, H. B. *J. Organomet.Chem.* **1983**, *250*, 227. (d) Nelsen, S. F.; Kapp, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 1265. (e) Schönberg, A.; Mustafa, A. *Chem. Rev.* **1947**, *40*, 181. (f) Popp, F. D.; Schultz, H. P. *Chem. Rev.* **1962**, *62*, 19. (g) Mukaiyama, T.; Sato, T.; Hanna, J. *Chem. Lett.* **1973**, 1041.

(2) Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1989; Vol. 3, p 721.

(3) (a) Dubois, J. E.; Bauer, P. *J. Am. Chem. Soc.* **1968**, *90*, 4510, 4511. (b) Pilkington, J. W.; Waring, A. J. *Tetrahedron Lett.* **1973**, *44*, 4345. (c) Stiles, M.; Mayer, R. P. *J. Am. Chem. Soc.* **1959**, *81*, 1497. (d) Nakamura, K.; Osamura, Y. *Tetrahedron Lett.* **1990**, *31*, 251.

(4) Nakamura, K.; Osamura, Y. *Tetrahedron Lett.* **1990**, *31*, 251.

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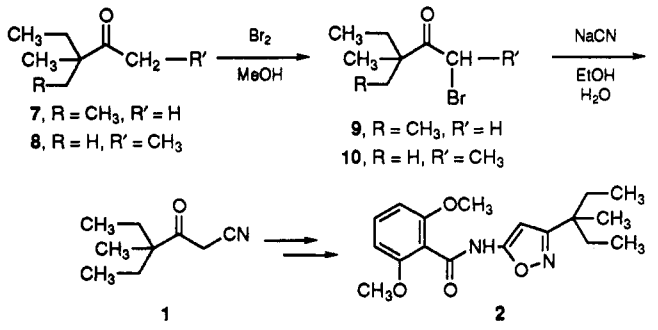
Scheme II



the rate-determining step.[5] For unbranched ketones such as 2-butanone, the methylene is deuteriated faster indicating the rate of enolization to the methylene to be slightly favored over that toward the methyl group.[6] However, deuteriation of methyl ketones flanked with a branched substituent was much slower. The presence of α-branching is known to result in more rapid enolization at the less substituted site,[6] perhaps due to destabilization of the enol or to the steric requirements of nucleophilic attack. The differences between protonation and bromination are generally small. It was also assumed that rearrangements allowing equilibration of the bromo ketones **9** and **10** were not occurring under these conditions.[7] On this basis, it was therefore expected that methyl ketone **7** might brominate somewhat faster than ethyl ketone **8**.[8]

When the mixture of **9** and **8** was reacted with NaCN in aqueous EtOH[9] at reflux, only the α-bromomethyl ketone **9** reacted forming keto nitrile **1**. Extraction of keto nitrile **1** into aqueous base (pH = 10) allowed facile separation from the neutral contaminant **8**. Acidification and extraction then provided 4-ethyl-4-methyl-3-oxohexanenitrile (**1**) in 92% yield. Reaction of **1** with hydroxylamine, under careful pH control as previously described, produced the intermediate isoxazolamine, condensation of which with 2,6-dimethoxybenzoyl chloride provided Isoxaben (**2**).[10]

Experimental Section

General Experimental Procedures. Melting points were determined on a hot-stage microscope and are uncorrected. All experiments were conducted under an atmosphere of nitrogen, unless otherwise noted, and monitored by thin-layer chromatography using Merck F254 silica gel plates. All solvents and reagents were used as obtained. ^{1}H and ^{13}C NMR spectra were measured at 300 MHz in $CDCl_3$ with tetramethylsilane as an internal standard. Microanalyses were conducted by the Physical Chemistry Department of Lilly Research Laboratories.

3,4-Dimethyl-3,4-hexanediol (3). Methyl ethyl ketone (50.0 g, 0.69 mol) was dissolved in THF (430 mL) and cooled to −60 °C under N_2. $TiCl_4$ (195 g, 1.0 mol) was then added dropwise with stirring over 20 min. To the resulting yellow slurry was then added Zn dust (135 g, 2.0 mol) portionwise at a rate to maintain constant stirring. Upon complete addition, the cooling bath was removed and the reaction mixture was brought to reflux. The thick dark brown-black reaction mixture was heated under reflux for 3.0 h and then cooled to ambient temperature. A 20% aqueous K_2CO_3 (50 mL) solution was added with continued stirring for 15 min, followed by the addition of Et_2O (500 mL) and H_2O (1 L). The precipitate was removed by filtration (using Celite) and rinsed with additional Et_2O. The aqueous phase was extracted with Et_2O (3 × 100 mL) and the combined organic phase rinsed with water (150 mL), dried (Na_2SO_4), and concentrated to a clear yellow oil (49.5 g, 99%): bp 68–70 °C (1 mmHg); R_f 0.35 (SiO_2, Et_2O/petroleum ether 1:1); ^{1}H NMR δ 0.92 (t, 6H, J = 7.7 Hz), 1.1 (d, 6H, J = 5.8 Hz), 1.33–1.50 (m, 2H), 1.55–1.75 (m, 2H); ^{13}C NMR δ 8.1, 8.1, 19.9, 20.3, 28.2, 28.5, 84.2, 84.3; IR ($CHCl_3$) 3560, 3456, 2979, 2944, 1461, 1381 cm^{-1}; HRMS (LiI FAB matrix) calcd for $C_8H_{18}O_2Li$ 153.1467, found 153.1464.

3-Ethyl-3-methyl-2-pentanone (7). The diol **3** (50 g, 0.35 mol) was cooled to −40 °C, and concd H_2SO_4 (413 g, 4.2 mol) was then added over 1 h. The resulting thick yellow reaction mixture was slowly warmed to −10 °C over the next 1 h. The reaction mixture was poured onto crushed ice (500 g) and Et_2O (300 mL) with external cooling. The mixture was stirred for 1 h. The aqueous phase was extracted with Et_2O (2 × 100 mL), and the combined organic phase was washed successively with $NaHCO_3$ (2 × 150 mL), dried over Na_2SO_4, and concentrated to give **7** as a clear yellow oil (41 g, 90%): bp 35–37 °C (8 mmHg); ^{1}H NMR δ (desired methyl ketone) 0.77 (t, 3H, J = 7.2 Hz), 1.02 (s, 3H), 1.44 (sextet, 2H, J = 7.2 Hz), 1.62 (sextet, 2H, J = 7.2 Hz), 2.08 (s, 3H); (undesired ethyl ketone) 0.78 (t, 3H, J = 7.2 Hz), 1.01 (t, 3H, J = 7.2 Hz), 1.08 (s, 6H), 1.55 (q, 2H, J = 7.2 Hz), 2.48 (q, 2H, J = 7.2 Hz); ^{13}C NMR δ (desired methyl ketone) 8.7, 19.7, 30.8, 32.6, 52.1, 205.6; (undesired ethyl ketone) 7.7, 8.7, 23.6, 29.5, 32.4, 47.3, 215.5; UV (EtOH) λ_{max} 243 nm; IR (desired methyl ketone, $CHCl_3$) 2972, 2940, 1699, 1463, 1357 cm^{-1}; MS m/z (M^+) 128; UV (EtOH) λ_{max} (abs) 243 nm (0.488); HRMS (EI) calcd for $C_8H_{16}O$ 128.1201, found 128.1201.

1-Bromo-3-ethyl-3-methyl-2-pentanone (9). Ketone **7** (5.7 g, 0.0445 mol) was dissolved in MeOH (90 mL) and then cooled to −5 °C under nitrogen. Br_2 (10.66 g, 0.0667 mol) was added dropwise via syringe using a Teflon needle over 5 min. The orange-red solution was stirred at 0 °C for 3 h, H_2O (16 mL) was added, and the mixture was stirred for another 1.5–2.0 h. H_2O (100 mL) and Et_2O (100 mL) were then added. The aqueous phase was extracted with Et_2O (3 × 50 mL), and the combined organic phase was washed with saturated K_2CO_3 (100 mL), dried over Na_2SO_4, and concentrated to a light brown oil (9.2 g, 100%): R_f 0.75 (SiO_2, hexane/EtOAc/CH_2Cl_2, 3:1:1); ^{1}H NMR δ 0.8 (t, 6H, J = 7.7 Hz), 1.15 (s, 3H), 1.45–1.60 (m, 2H), 1.6–1.75 (m, 2H), 4.15 (s, 2H); ^{13}C NMR δ 8.7, 19.7, 30.9, 32.8, 52.1, 205.6; MS m/z 206 (M − 1), 208 (M + 1); IR ($CHCl_3$) 2974, 1722, 1464, 1387 cm^{-1}. Anal. Calcd for $C_8H_{15}OBr$: C, 46.40; H, 7.30. Found: C, 46.64; H, 7.44.

4-Ethyl-4-methyl-3-oxohexanenitrile (1). Bromo ketone **9** (1.10 g, 5.3 mmol), 2:1 EtOH/H_2O (8.5 mL) and KCN (1.04 g, 15.9 mmol) were stirred at ambient temperature for 5 min and then at reflux for 30 min. After the mixture was cooled, the solvent was removed *in vacuo* (<30 °C) and the residue was stirred vigorously with 2 N KOH (20 mL) and Et_2O (20 mL). The organic phase was extracted with 2 N KOH solution (3 × 20 mL). The combined aqueous layer was acidified with 2 N HCl to pH = 1 with external cooling and then extracted with EtOAc (4 × 20 mL). The organic phase was dried (Na_2SO_4) and concentrated to yield **1** as a dark brown oil, 0.75 g (92%): R_f 0.57 (SiO_2, hexane/EtOAc/CH_2Cl_2, 3:1:1); ^{1}H NMR δ 0.8 (t, 6H, J = 7.7 Hz), 1.1 (s, 3H), 1.45–1.75 (m, 4H), 3.59 (s, 2H); ^{13}C NMR δ 8.3, 19.1, 27.7, 30.0, 52.0, 114.0, 202.4; UV (EtOH) λ_{max} 264, 233 nm. Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.54; H, 9.90; N, 9.06.

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(5) Dubois, J. E.; Toullec, J. *J. Chem. Soc., Chem. Commun.* **1969**, 478.
(6) Rappe, C.; Sachs, W. H. *J. Org. Chem.* **1967**, *32*, 3700.
(7) Mehta, M. D.; Miller, D.; Tidy, D. J. D. *J. Chem. Soc.* 1963, 4614.
(8) Gaudry, M.; Marquet, A. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. VI, p 193.
(9) Marvel, C. S.; McColm, E. M. *Organic Syntheses;* Wiley: New York, 1941; Collect. Vol. I, p 536.
(10) Private communication, Pressler, R. E., Lilly Research Laboratories.