The Preparation of Highly Branched Ketones and Alcohols

By W. A. Mosher, P. W. Berger, A. P. Foldi, J. E. Gardner, T. J. Kelly, and C. Nebel,* Department of Chemistry, University of Delaware, Newark, Delaware 19711

A procedure is described for the preparation of highly branched ketones and alcohols with the general formulae R²R³R⁴C·CHR⁵·CO·R¹ and R²R³R⁴C·CHR⁵·CR⁶(OH)R¹. The multi-step route involves classical synthetic methods which give good yields. R may be varied and can be either alkyl or aryl.

THE study of molecular rearrangements in aliphatic carbonium ions has necessitated the preparation of highly branched alcohols; a multi-step synthesis has been developed for this purpose. Classical synthetic methods fail for alcohols which possess a large steric requirement; use of both Grignard and alkyl-lithium reagents often leads to reduction and fragmentation reactions in such cases.

 \cap

A general synthesis has been developed for ketones and alcohols with structures (I) and (II). The only structural requirement is for an α -hydrogen atom in the product.

 $\begin{array}{ccc} R^2 R^3 R^4 C \cdot CHR^5 \cdot CO \cdot R^1 & R^2 R^3 R^4 C \cdot CHR^5 \cdot CR^6 (OH) R^1 \\ (I) & (II) \\ R = H, \ alkyl, \ or \ aryl \end{array}$

The synthesis of the ketone involves five steps, all of which give good yields. A different R group can be introduced at each step; thus a large number of ketones and alcohols can be prepared. This method is useful for the introduction of ¹⁴C-labelled groups, since there is no possibility of radioactive scrambling at any point. Although five steps are involved in the preparation of a ketone, some steps do not require isolation or purification of the intermediate. The reaction sequence is summarised in the Scheme. An alternative procedure, re-

¹ W. H. Saunders and G. L. Carges, J. Amer. Chem. Soc., 1960, 82, 358.

² M. F. Ansell, J. W. Hancock, and W. J. Hickinbottom, J. Chem. Soc., 1956, 911.

corded by Saunders and Carges,¹ is not as versatile, requires more steps, and gives lower yields. Highly branched ketones have also been prepared by the Rupe rearrangement, but this method also yields isomeric side products.²



Step (i) uses the Knoevenagel condensation of ethyl cyanoacetate with various aldehydes and ketones to give ethyl alkylidene-cyanoacetates in relatively high yields.

TABLE 1

$R^{2}R^{3}R^{4}C \cdot CR^{5}(CN) \cdot CO_{2}Et$ prepared by step (iii)

				Vield		Fo	ound (%)		Req			
\mathbb{R}^2	\mathbb{R}^3	\mathbb{R}^4	R^5	(%)	B.p.°/mm.	С	\mathbf{H}	Ν	Formula	С	Η	Ν	Comment
н	Me	Me	Et	82	112-113.5/15 (lit., a 109°/15)				$C_{10}H_{17}O_{2}N$				
Me	${\rm Me}$	\mathbf{Ph}	Me	94	125 - 127/0.3	73.50	7.73	5.96	$C_{15}H_{19}O_{2}N$	73.44	7.81	5.71	
Me	Me	Ph	Et	74	$151 - 152/2 \cdot 75$	73.85	8.07	5.63	$C_{16}H_{21}O_{2}N$	74·10	8.16	5.40	G.l.c. on carbowax 20m shows 98% purity
н	Me	\mathbf{Ph}	Et	48	$141 - 142/2 \cdot 5$	73.57	7.96	5.60	$C_{15}H_{19}O_{2}N$	73.44	7.81	5.71	_
н	Me	Me	\mathbf{Ph}	41 ^b	100—104/0·3	73.24	7.64		$C_{14}H_{17}O_{2}N$	72.70	7.41		n_D^{25} 1.4939; G.l.c. on Ucon polar 220° shows 99% purity
н	Me	\mathbf{Ph}	\mathbf{H}	73	$125 - 126/1 \cdot 0$	71.59	6.73	6.92	$C_{13}H_{15}O_{2}N$	71.89	6.98	6.95	
Et	Me	\mathbf{Ph}	н	64	$167 - 168 / 5 \cdot 0$	73.48	7.77	5.97	$C_{15}H_{19}O_2N$	73.44	7.81	5.71	
\mathbf{Et}	Me	\mathbf{Ph}	\mathbf{Et}	82	123 - 124 / 0.50	75.00	8.43	5.37	$\mathrm{C_{17}H_{23}O_{2}N}$	74.69	8.48	5.12	
Et	Me	\mathbf{Ph}	Me	46	120 - 121 / 0.50	74.10	8.16	5.40	$C_{16}H_{21}O_2N$	71.03	8.17	5.62	

^a E. Fischer, A. Rohde, and F. Brauns, Annalen, 1914, **402**, 364. ^b Prepared by alkylation of phenylcyanoacetate with 2-bromopropane.

TABLE 2

R²R³R⁴C·CHR⁵·CN prepared by step (iv)

				Vield		$\mathbf{F}\mathbf{c}$	ound (?	%)		Rec			
\mathbb{R}^2	\mathbb{R}^3	\mathbb{R}^4	\mathbb{R}^{5}	(%)	B.p.°/mm.	С	н	Ν	Formula	С	н	Ν	Comment
Me	${\rm Me}$	Me	Me	69	154-156/760 (lit. a 150-150.5/760)				$\rm C_7H_{13}N$				
Me	Me	Me	Et	68	103/89	76.48	12.27	11.01	$C_8H_{15}N$	76.24	12.08	11.19	
н Н	Me Me	Me Et	Et H	80 80	90-92/90 $99-99\cdot5/92$ (1;+ b 156 158/760)	75.69	12.03	12.85	$C_{7}H_{13}N C_{6}H_{11}N$	79.01	11.79	12.00	
Me	Me	\mathbf{Ph}	Me	92	105/1.4	83.19	8.73	8.09	C12H15N	83·26	8.89	9.10	n _D ²⁶ 1.5130
Me	Me	Ph	Et	89	$118 - 119/2 \cdot 75$	83.02	8.95	7.62	$C_{13}^{12}H_{17}^{13}N$	83.37	9.15	7.48	G.l.c. on Ucon polar shows a purity of 97%
н	Me	Me	Ph	65	118—122/11 (lit.,° 245—249/765)				$C_{11}H_{13}N$				M.p. 111 (from pen- tane); G.l.c. on Ucon polar 220° shows 99% purity
Et	Me	\mathbf{Ph}	Et	92	90 - 91/0.35	83.78	9.30	7.20	C14H10N	83.53	9.51	6.96	Shows by /o pulley
Et	Me	\mathbf{Ph}	Me	90	86—87/0·3 0	83.50	9.40	7.63	$C_{13}H_{17}N$	83.37	9.15	7.48	

^a C. G. Overberger and M. D. Berenbaum, J. Amer. Chem. Soc., 1952, 74, 3293. ^b K. Ziegler and H. Ohlinger, Annalen, 1932, 495, 84. ^c F. Bodroux and F. Taboury, Bull. Soc. chim. France, 1910, [4] 7, 668.

TABLE 3

R²R³R⁴·CHR⁵·CO·R¹ prepared by step (v)

	Yield			Yield		M.p. of	Found	d (%)	Reqd. (%)				
\mathbb{R}^1	\mathbb{R}^2	\mathbb{R}^3	\mathbb{R}^4	\mathbf{R}^{5}	(%)	B.p.°/mm.	derivative a	С	H	Formula	С	н	Comment
Me	Me	Me	Me	Me	97	148 - 154/760	D, 112—113°			C_8H_{16}			
						(lit., ¹ 78—79·5/77)	(lit., 1112.5 - 113)						
Me	Me	Me	Me	\mathbf{Et}	59	82 - 85/50	S, 155—156	75.98	12.75	C ₉ H ₁₈ O	75.99	12.76	
Εt	Me	Me	Me	Me	70	84/49	S, 123-124	75.98	12.55	C ₉ H ₁₈ O	75.99	12.76	
						(lit.,* 87/50)	(lit.,* 99—100)	60.30	10.55	C ₁₀ H ₁₉ N ₃ O ^b	60.03	10.73	
Me	н	Me	Me	Et	72	8890//99	S. 121—122			C ₀ H ₁₆ O			
						(lit., 10 154-155/760)	(lit., † 121.5)			8 10			
Me	н	Me	Et	Me	76	90/90	S. 135-136			C ₈ H ₁₆ O			
						(lit., ¹² 136.5—137.5/760)	(lit., ¹² 137.5)			5 10			
Me	Me	Me	\mathbf{Ph}	Me	85	72 - 75/0.15	$\dot{D}, 124-125'$	61.62	6.11	C10H22N4O4 °	61.61	5.99	
Me	Me	Me	\mathbf{Ph}	\mathbf{Et}	46	9394/1	D, 118.5—119	82.62	10.15	C ₁₄ H ₂₀ O	82.30	9.87	
Me	\mathbf{H}	Me	Me	\mathbf{Ph}	21	107/11		82.05	9.01	C ₁ ,H ₁ ,O	81.77	9.15	$n_{\rm D}^{25} 1.4975$
Me	H	Me	\mathbf{Ph}	\mathbf{Et}	21 d	8990/1.0	D. 158—159	61.53	6.26	C ₁₀ H ₂₀ N ₄ O ₄ ^c	61.61	5.99	
\mathbf{Ph}	\mathbf{H}	Me	Me	\mathbf{Et}	52	8384/1.0	D, 116—117	81.51	9.43	$C_{13}H_{18}O$	82.05	9.54	

^a S = Semicarbazone; D = 2,4-dinitrophenylhydrazone. ^b Elemental analysis of semicarbazone. ^c Elemental analysis of 2,4-dinitrophenylhydrazone. ^d Product purified by preparative v.p.c. on a 20 ft. SE-30 column. * M. B. Green and W. J. Hickinbottom, J. Chem. Soc., 1957, 3262. [†] C. D. Nenitzescu and I. P. Canterniari, Ber., 1932, 65, 1449. Cope and his co-workers 3,4 have condensed 27 different aldehydes and ketones with ethyl cyanoacetate and obtained yields in the range 75-87%. Sufficient branching of the carbon chain in the ketone employed retards or inhibits condensation.³⁻⁶ The condensation of acetone with ethyl cyanoacetate has been improved by the use of ammonium acetate as catalyst; yields are in the range 85-90%.

Step (ii) depends upon the nature of \mathbb{R}^3 . If $\mathbb{R}^3 = \mathbb{H}$, it involves catalytic hydrogenation of the double bond with platinum or palladised charcoal. Yields from 90 to 97% were reported by Cope and his co-workers.^{3,4} If \mathbb{R}^3 = alkyl or aryl, a Grignard reagent is added across corresponding ketones (46–97%). Attempts to prepare the first compound in Table 3 by the acetoacetic ester synthesis (alkylation of ethyl methylacetoacetate with a t-butyl halide followed by hydrolysis and decarboxylation) were unsuccessful.¹⁰ The fourth compound in Table 3 has been previously prepared by the above mentioned method, but the yields are poor and the reaction sequence is experimentally difficult.¹¹ The fifth ketone has also been previously prepared by the Cope rearrangement but this method employs a greater number of steps and the yields are lower.¹² The ketones can be reduced, step (vi) to yield secondary alcohols where $R^6 = H$ or they can react with alkyl or aryl

TABLE 4	
R ² R ³ R ⁴ C·CHR ⁵ ·CR ⁶ (OH)R ¹ prepared by step	(vi)

											-					
	Yield							M.p. of Found (%)			Required (%)					
R1	\mathbf{R}^2	\mathbb{R}^3	\mathbb{R}^4	\mathbf{R}^{5}	\mathbf{R}^{6}	(%)	B.p.°/mm.	derivative a	С	н	Ν	Formula	С	н	Ν	Comment
Me	Me	Me	Me	Me	Н	86	9294/67 ^b	P, 74-75° ^b	71.90	9.04	5.75	C ₁₅ H ₂₃ NO ₂ ^b *	72.25	9.30	5.62	$n_D^{25} 1.4311$
							(lit., ¹ 93—95/67)	P, 73·5—74 °	71.97	9.41	5.69	C ₁₅ H ₂₃ NO ₂ ^b *	72.25	9.30	5.62	$n_{\rm D}^{25} 1.4349$
					~ ~	~-	100—101/67 °	T				a				
Me	Me	Me	Me	Et	Н	67	$73 - 75/12^{a}$	P, 8889				$C_2H_{20}O$				
							$(lit.,^2 66/12)$	(lit.,* 89·5)								
Et	Me	Me	Me	Me	\mathbf{H}	70	$68 - 72/16^{d}$	D, 7684 d	75.25	14.06	5	C ₉ H ₂₀ O	75.00	13.88		
Me	Η	Me	Me	Et	Me	55 e	$72 \cdot 5/18$		74.67	13.74	L ·	$C_9H_{20}O$	75.00	13.88		
Me	\mathbf{H}	Me	\mathbf{Et}	Me	Me	38 °	74/14					$C_9H_{20}O$				
							(lit., 57-58/5)									
Me	Me	Me	\mathbf{Ph}	Me	Η	92	$99-102/1.15^{d}$		81.24	10.09)	C13H20O	81.20	10.48		$n_{\rm D}^{25} 1.5276$
Me	Me	Me	\mathbf{Ph}	Et	Н	95	101 - 102/1	P, 93—94	81.95	10.60)	$C_{14}H_{22}O$	81.55	10.66		

^a D = 3,5-Dinitrobenzoate; P = phenylurethane. ^b Low-boiling isomer. ^c High-boiling isomer. ^d Mixture of two possible diasteroisomers. ^e Prepared by the addition of methyl Grignard to the ketone. ^f J. Colonge, Bull. Soc. chim. France, 1935, [5] 2, 754

* Elemental analysis of phenylurethane derivative.

the activated double bond to give yields from 42-75%. The Grignard reagent will add only across the double bond and will not attack either the nitrile or the ester group, despite the fact that it is used in excess. The reaction fails or the yields are extremely low when \mathbb{R}^3 is highly branched, e.g. s- or t-butyl.⁷⁻⁹

If $R^5 = H$, step (iii) can be eliminated. In cases where $R^5 = alkyl$ or aryl, the cyano-ester must be alkylated by addition of the appropriate alkyl or aryl halide to the sodium salt, to give yields in the range 71-94%. Addition of isopropyl bromide gave only a 41% yield since its steric requirements are greater. A competitive side reaction, the elimination of hydrogen bromide from isopropyl bromide in the presence of base, may also account for the decreased yield. The product from this step need not be purified (Table 1).

Hydrolysis and decarboxylation, step (iv), can readily be accomplished by heating the ester under reflux in ethylene glycol in the presence of potassium hydroxide (yields 65-92%) (Table 2).

The addition of alkyl or aryl Grignard reagents to the nitrile, step (v), and subsequent hydrolysis, yields the

³ A. C. Cope, J. Amer. Chem. Soc., 1937, 59, 2327.
⁴ A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, J. Amer. Chem. Soc., 1941, 63, 3452.
⁵ F. S. Prout, J. Org. Chem., 1953, 18, 928.
⁶ G. Jones, Org. Reactions, 1967, 15, 204.

⁷ E. P. Kohler and M. Reimer, Amer. Chem. J., 1905, 33, 333.

Grignard reagents to yield tertiary alcohols (Table 4). Some of the alcohols formed are capable of existing in diastereoisomeric forms, since they contain two asymmetric centres. In the case of 3,4,4-trimethylpentan-2-ol the two forms were completely separated by distillation.

EXPERIMENTAL

M.p.s are corrected. N.m.r. spectra (p.p.m. from internal tetramethylsilane) were determined with a Varian A-60A spectrometer for solutions in carbon tetrachlorde. Carbon and hydrogen analyses were performed by Micro-Analysis Inc., Wilmington, Delaware.

The following syntheses of 3-ethyl-4-methyl-4-phenylpentan-2-one and 3-ethyl-4-methyl-4-phenylpentan-2-ol are typical. Other compounds made are described in the Tables.

Ethyl 2-Cyano-3-methylbut-2-enoate; step (i).--Acetone was condensed with ethyl cyanoacetate in benzene-acetic acid.⁴ Ammonium acetate was the best catalyst. The best yield (89%) is obtained when the molar ratio of the reagents in the order mentioned above is 1.37: 1.00: 1.03: 0.206: 0.103. The product had b.p. 116-120°/15 mm. (lit.,¹³ b.p. 114-116°/14 mm. yield 54%).

⁸ E. R. Alexander, J. D. McCollum, and D. E. Paul, J. Amer. Chem. Soc., 1950, 72, 4791. ⁹ F. S. Prout, J. Amer. Chem. Soc., 1952, 74, 5915.

- ¹⁰ J. W. Baker, J. Chem. Soc., 1950, 1302. ¹¹ L. Clark, Amer. Chem. J., 1908, **39**, 572.
- 12 A. C. Cope, C. M. Hofmann, and E. M. Hardy, J. Amer.,
- Chem. Soc., 1941, 63, 1852.
- ¹³ I. Vogel, J. Chem. Soc., 1928, 2010.

Ethyl 2-Cyano-3-methyl-3-phenylbutanoate; step (ii). Addition of phenyl Grignard reagent across the activated double bond of ethyl 2-cyano-3-methylbut-2-enoate⁸ gave the saturated ester (68%), b.p. 132–135°/1·2 mm., $n_{\rm D}^{20}$ 1·5072 (lit.,⁸ yield 60%, b.p. 155°/0·5 mm., $n_{\rm D}^{20}$ 1·5069).

Ethyl 2-Cyano-2-ethyl-3-methyl-3-phenylbutanoate; steð (iii).-To sodium ethoxide [sodium (34.5 g., 1.50 mole) in absolute ethanol (664 ml.)] was added ethyl 2-cyano-3-methylbutanoate (204 g., 0.88 mole) during 30 min.; the solution was then stirred and heated under reflux for 1 hr. It was cooled to 0° and bromoethane (164 g., 1.51 moles) was added during 1 hr. The resulting dark yellow solution was stirred and heated under reflux for an additional 12 hr., cooled to room temperature, and treated with water (1 1.) saturated with sodium chloride. The aqueous layer was extracted with ether and the extract was dried (Na_2SO_4) . The solvent was removed and the residue was vacuumdistilled through a packed column (1 ft.) to give the product (169 g., 74%), b.p. 151-152°/2·75 mm. (Found: C, 73·85; H, 8.05; N, 5.65. C₁₆H₂₁NO₂ requires C, 74.1; H, 8.15; N, 5.4%), >98% pure (g.l.c. on Carbowax 20 M and Ucon polar). Use of sodium ethoxide rather than sodamide gave higher yields.

2-Methyl-2-phenylpentane-3-carbonitrile; step (iv).--Ethyl 2-cyano-2-ethyl-3-methyl-3-phenylbutanoate (102 g., 0.39 mole) was added to a solution of potassium hydroxide (43.6 g., 0.78 mole) ethylene glycol (176 g., 2.89 moles). The solution was heated under reflux for 5 hr. at 118° during which time a dark yellow solution formed which separated into two layers. When cool, it was diluted with water (175 ml.) and extracted with ether. The extracts were washed with water and dried (Na_2SO_4) . Solvent was removed and the residue was vacuum-distilled through packed column (1 ft.) to give the product (64.5 g., 89%). b.p. 118-119°/2·75 mm., >97% pure [g.l.c. on Ucon polar (20 ft.)] (Found: C, 83.0; H, 8.95; N, 7.6. C₁₃H₁₇N requires C, 83·35; H, 9·15; N, 7·5), δ (CCl₄) 1·03 [t, C(5)H₃], 1.30 [m, $C(4)H_2$] 1.43 [s, $C(1)H_3$ and C(2)Me] 2.60 [m, C(3)H], and 7.26 (m, Ph).

J. Chem. Soc. (C), 1969

3-Ethyl-4-methyl-4-phenylpentan-2-one; step (64.5 g., 0.34 2-Methyl-2-phenylpentane-3-carbonitrile, mole) was added during 1 hr. to methylmagnesium iodide (0.67 mole) in ether. The ether was displaced with tetrahydrofuran and the solution was heated under reflux for 3 days at 60° before the resulting imine salt was hydrolysed with 10% hydrochloric acid. The solution was steamdistilled for 8 hr. and the distillate was extracted with ether. The extracts were dried (Na_2SO_4) , the ether was removed, and the residue was vacuum-distilled through a packed column (1 ft.) to yield the product (31.6 g., 45.5%), b.p. 93.4°/1.0 mm. and some unchanged starting material; δ (CCl₄) 0.72 [t, C(3)-CH₂·CH₃], 1.33 [d, J 2 c./sec., C(4)Me and (5)H₃], 1.67 [s, C(1)H₃], 1.75 [m, C(3)·CH₂], 2.74 [dd, J 3 c./sec., C(3)H], and 7.21 (m, Ph) (Found: C, 82.6; H, 10.15. C₁₄H₂₀O requires C, 82.3; H, 9.85%); 2,4-dinitrophenylhydrazone, m.p. 118.5-119°.

3-Ethyl-2-methyl-4-phenylpentan-2-ol; step (vi).-3-Ethyl-4-methyl-4-phenylpentan-2-one (31.6 g., 0.155 mole) in anhydrous ether (50 ml.) was reduced with lithium aluminium hydride (2.2 g., 0.058 mole). The mixture was heated under reflux for 5 hr., then hydrolysed with aqueous ethanol. The aqueous portion was extracted several times with ether and the combined extracts were dried (Na_2SO_4) . Removal of the solvents under reduced pressure and vacuum-distillation through a packed column (1 ft.) gave the product (30.4 g., 95%), b.p. 101-102°/1.0 mm.), δ (CCl₄), 0.89 [t, C(3)·CH₂·CH₃], 1.00 [d, C(1)H₃], 1.28 [d, J 2 c./sec., C(5)H₃ and C(4)Me], 1·41 [m, C(3)·CH₂], 1·72 [m, C(3)H], 3.72 [m, C(2)H], and 7.21 (m, Ph) [Found: C, 81.5; H, 10.6%; M (mass spec.), 206. C₁₄H₂₂O requires C, 81.55; H, 10.65%; M, 206]; phenylurethane, m.p. 93-94° (Found: C, 77.55; H, 8.4. C₂₁H₂₇NO₂ requires C, 77.55; H, 8.3%).

This work was supported in part by grants from the Sun Oil Co., and E. I. DuPont de Nemours Co., for which thanks is expressed.

[8/573 Received, April 19th, 1968]