CHEMISTRY LETTERS, pp. 1109-1112, 1988.

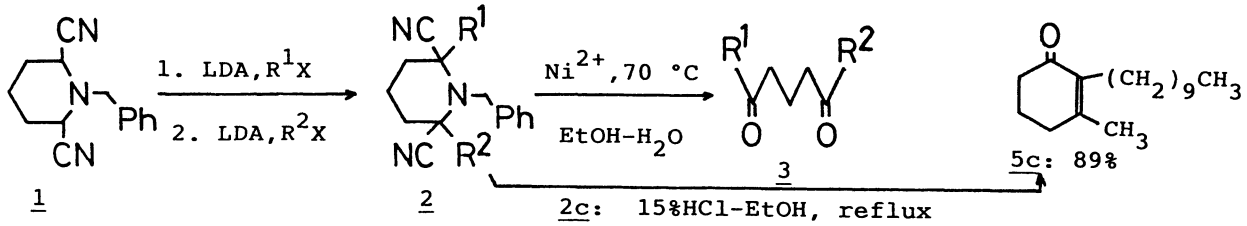
1-Benzyl-2,6-dicyanopiperidines as a New Class of Annelating Reagents. Use for Preparation of Fused Polycyclic Compounds

Kazumasa TAKAHASHI,* Mikio ASAKAWA, and Katsuyuki OGURA
Department of Synthetic Chemistry, Faculty of Engineering,
Chiba University, Yayoi-cho, Chiba 260

The utility of 1-benzyl-2,6-dialkyl-2,6-dicyanopiperidines as an annelating reagent, i.e. latent 1,5-diketones, is demonstrated in synthesis of multi-fused compounds.

Cyclization of unsymmetrical 1,5-diketones (3) is an important route to synthesis of polycyclic natural products. Several synthetic routes to 3 have been reported: Methyl vinyl ketones,[2] 6-methyl-2-vinylpyridine,[3] and vinylsilanes[4] have been used as starting materials. The exploration of more conventional starting materials has been continued for preparation of multi-fused compounds. For the construction of cyclohexenone skeletone, an intramolecular condensation of 1,5-diketones is expected to be the most simple and efficient method, while many of synthetic methods of 1,5-diketones require starting materials which are difficult to synthesize and to handle. However, 1-benzyl-2,6-dicyanopiperidine (1) used as a starting material in this work is simply synthesized,[1] and the present method using 1 easily gives various unsymmetrical 1,5-diketones (3): Hydrolysis of unsymmetrical 1-benzyl-2,6-dialkyl-2,6-dicyanopiperidines (2), which are intermediates of synthesis of unsymmetrical 2,6-dialkylpiperidine alkaloids using 1 reported in a previous paper,[1] is found to give unsymmetrical 1,5-diketones (3) in good yields. There is, moreover, no information for preparation of unsymmetrical 1,5-diketones 3 using 1. We report here an efficient synthetic method of unsymmetrical 1,5-diketones 3 using 1 and a practical application of 3 to preparation of fused polycyclic compounds.

The alkylation of 1 selectively gave mono-alkylated products, 2-alkyl-1-benzyl-2,6-dicyanopiperidines. The selective mono-alkylation is important for the subsequent preparation of unsymmetrical dialkylated products (2). Preparation of 6-methyl- and 6-n-propyl-1-benzyl-2,6-dicyano-2-undecylpiperidines (2c and 2d)



Scheme 1. Dialkylation of 1 and hydrolysis of 2,6-dialkylated piperidines (2).

Table 1. Preparation of 2 and 3

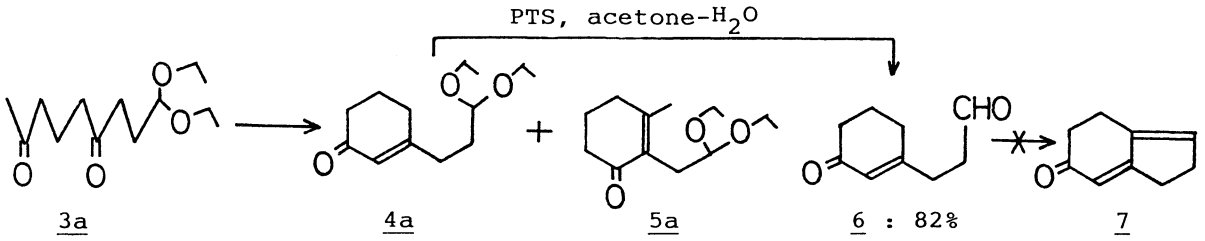
Products	Yield/%	
	2	3
a: R^1= CH_3, R^2= $CH_2CH_2CH(OC_2H_5)_2$	67[a]	77
b: R^1= CH_3, R^2= $CH_2CH_2CH_2(CH_3)C<^{O}_{O}]$	50[b]	48[c]
c: R^1= CH_3, R^2= $(CH_2)_{10}CH_3$	85	92
d: R^1=$CH_2CH_2CH_3$, R^2= $(CH_2)_{10}CH_3$	86	73

a) Not isolated as a pure compound. b) Not isolated.
c) Over-all yield from 1.

used in the present work has been reported.[1] According to the similar procedure, the one-pot reaction of 1 with methyl iodide and then 3-chloro-1,1-diethoxypropane gave 1-benzyl-2,6-dicyano-2-(3,3-diethoxypropyl)-6-methylpiperidine (2a) in 67% overall yield from 1. Isolation of 2a was attempted by means of column chromatography using Florisil, but 2a was obtained as a mixture with two minor products, i.e. 1-benzyl-2,6-dicyano-2,6-dimethylpiperidine and 9,9-diethoxy-2,6-nonanedione (3a) formed by hydrolysis of 2a on the column. Accordingly, the yield of 2a was estimated from the ^{1}H-NMR spectrum of the eluated mixture. Likewise, the one-pot reaction of 1 with methyl iodide and then 5-chloro-2-pentanone ethyleneacetal gave a brown oil. The presence of 1-benzyl-2,6-dicyano-2-(4,4-ethylenedioxypentyl)-6-methylpiperidine (2b) was confirmed from the ^{1}H-NMR spectrum of the brown oil, but the unstability of 2b on the column was responsible for the failure of purification. Consequently, the brown oil itself was used in the subsequent hydrolysis.

Hydrolysis of the dialkylated products, 2a, crude 2b, 2c, and 2d at 70 °C in an aqueous solution of nickel acetate containing ethanol, gave 9,9-diethoxy-2,6-nonanedione (3a), 2,6,10-undecanetrione-2-ethylene acetal (3b), 2,6-heptadecanedione (3c), and 4,8-nonadecanedione (3d) in 48%-92% yields (see Table 1). In order to maintain the acetal group of 2a and 2b, the hydrolysis should be carried out under neutral or basic conditions. Treatment of 2 in the present conditions was quite favorable for our synthetic purpose. Hydrolysis of 2c under gently refluxed conditions in an aqueous ethanolic solution of 15% hydrochloric acid afforded directly 2-decyl-3-methyl-2-cyclohexenone (5c) in 89% yield. It is obvious that the product 5c is obtained via intramolecular condensation of 1,5-diketone 3c, since the formation of 3c was noted in the initial period by means of thin-layer chromatography. In general, the condensation of 3 is expected to give two isomers. However, the hydrolysis of 2c gave only a single isomer, 5c. The selective formation of 5c is established at a thermodynamical level as described later.

Treatment of 3a with an aqueous ethanolic sodium hydroxide at 30 °C gave, in a combined yield of 91% after purification by chromatography, a 1:6 mixture of 3-(3,3-diethoxypropyl)-2-cyclohexenone (4a) and 2-(3,3-diethoxyethyl)-3-methyl-2-cyclohexenone (5a) (see Table 2). Treatment of 3a with a tetrahydrofuran (THF) solution of lithium hexamethyldisilazide (LHMDS) at -78 °C, on the other hand, gave a 19:1 mixture of 4a and 5a. This result constitutes a significant demonstration of preferential formation of β-monosubstituted cyclohexenone relative to

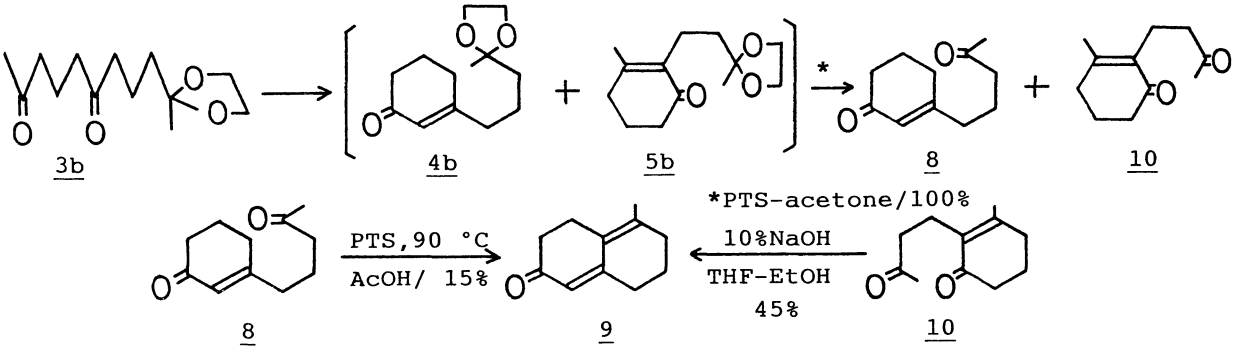


Scheme 2. Intramolecular condensation of 3a, 4a, and 6.

Table 2. Base and temperature effects on distributive ratio of products 4a:5a and 4b:5b

Conditions	Yield/ %			Ratio	Yield/ %			Ratio
	4a	5a	Total	4a:5a	4b	5b	Total	4b:5b
10%NaOH-EtOH, 30 °C	13	78	91	1:6	38	57	95	1:1.5
10%NaOH-EtOH, reflux for 25 min	-	-	-	-	20	52	72	1:2.6
LHMDS-THF, -78 °C	50	3	53	19:1	59	1	60	59:1

its α,β-disubstituted isomer from an internal aldolization reaction. Treatment of 4a with an acetone solution containing a trace of water and p-toluenesulfonic acid (PTS) at room temperature gave 3-(3-oxopropyl)-2-cyclohexenone (6) in 82% yield. The subsequent internal aldolization of 6 did not give any desirable product 7 under alkaline and acidic conditions. The effect of changing reaction conditions was also examined in base-induced aldolization of 3b: A mixture of 3-(4,4-ethylenedioxypentyl)-2-cyclohexenone (4b) and 2-(3,3-ethylenedioxybutyl)-3-methyl-2-cyclohexenone (5b) was obtained in a 1:1.5 ratio[5] with a combined yield of 95% at 30 °C using an aqueous ethanolic sodium hydroxide. When the reaction mixture was heated to reflux for 25 min., the ratio changed to a 1:2.6 with a combined yield of 72%, indicating a significant temperature effect on product distribution. When aldolization of 3b was carried out at -78 °C using LHMDS, β-monosubstituted 4b was predominantly obtained: The ratio changed to a 59:1 with a combined yield of 60%. We believe that the remarkable ratio of 59:1 is the first demonstration of selective formation of β-monosubstituted cyclohexenones. It was ascertained that β-monosubstituted cyclohexenones were actually formed at the kinetic level.[6] The interconversion from β-monosubstituted- to α,β-disubsti-



Scheme 3. Intramolecular condensation of 3b, 8, and 10.

Table 4. Physical properties of new compounds isolated in this work

Compd.	Mp/°C	IR, ν_{CO}/cm^{-1}	MS(70 eV)	^{1}H-NMR($CDCl_3$, 270 MHz)[a], δ units [ppm]
3a	oil	1720	244(M^+)	1.21(t,6H,J=7 Hz,CH_3x2), 2.15(s,3H,CH_3), 3.39-3.81(m,4H,OCH_2CH_3x2)
3b	oil	1720	242(M^+)	1.31(s,3H,CH_3), 2.13(s,3H,CH_3), 3.93(s,4H, $-OCH_2CH_2O-$)
3c	69-70	1720	268(M^+)	0.87(t,3H,J=6 Hz,CH_3), 2.10(s,3H,CH_3)
3d	71.5-72.5	1720	296(M^+)	0.90(t-like,6H,CH_3x2)
4a	oil	1665	228 (M^++2)	1.19(t,6H,J=7 Hz,CH_3x2), 4.45(t,1H,J=4 Hz, CH), 5.84(br-s,1H,=CH)
5a	oil	1665	226(M^+)	1.15(t,6H,J=7 Hz,CH_3x2), 1.98(s,3H,CH_3), 3.24-3.84(m,4H,OCH_2CH_3x2)
5c	oil	1670	-	0.89(br-s,3H,CH_3), 1.90(s,3H,CH_3)
6	oil	1720, 1670	-	5.84(br-s,1H,=CH), 9.80(s,1H,CHO)
8	oil	1717, 1675	-	2.14(s,3H,CH_3), 5.84(br-s,1H,=CH)
9	oil	1660	162(M^+)	1.88(s,3H,CH_3), 5.65(br-s,1H,=CH)
10	oil	1710, 1670	-	1.97(s,3H,CH_3), 2.13(s,3H,CH_3)

a) Only data of characteristic protons are listed.

tuted-cyclohexenones is precedented.[7] Hydrolysis of a mixture of 4b and 5b in an acetone solution of PTS quantitatively gave 3-(4-oxopentyl)-2-cyclohexenone (8) and 2-(3-oxobutyl)-3-methyl-2-cyclohexenone (10). The subsequent intramolecular condensation of 8 in acetic acid containing PTS at 90 °C and that of 10 in a THF-EtOH solution of 10% sodium hydroxide at room temperature gave 5-methyl-3,4,6,7,8-pentahydronaphtalen-2-one (9) (see Scheme 3).

The present method is found to be useful for the preparation of unsymmetrical 1,5-diketones, which can lead to synthesis of fused polycyclic compounds.

References

1) K. Takahashi, H. Kurita, K. Ogura, and H. Iida, J. Org. Chem., 50, 4368 (1985).
2) E. D. Bergmann, D. Ginsburg, and R. Pappo, Org. React., 10, 179 (1959).
3) S. Danishefsky, P. Cain, and A. Nagel, J. Am. Chem. Soc., 97, 380 (1975).
4) G. Stork and M. E. Jung, J. Am. Chem. Soc., 96, 3682 (1974).
5) The ratio of 4b:5b was estimated from ^{1}H-NMR spectrum of a mixture of 4b and 5b, and moreover confirmed by isolating 8 and 10 quantitatively formed by hydrolysis of the mixture in an acetone solution of PTS.
6) A. T. Nielsen and W. J. Houlihan, Org. React., 16, 47 (1968).
7) R. N. Lacey, J. Chem. Soc., 1960, 1639.

(Received March 12, 1988)