An Improved Enamine-Alkylation Procedure. Synthesis of 1-Benzyl-2-indanones and 1-Benzyl-2-tetralones

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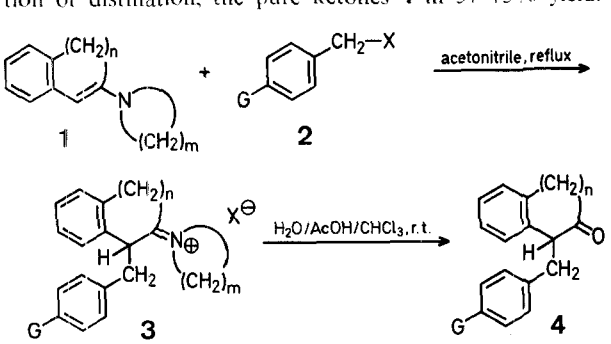
During the course of synthetic studies directed toward the preparation of homoalkaloids, need for the title compounds arose. However, the literature describes but two routes for their preparation, neither of which is convenient nor high-yielding. One method involves the alkylation of metal enolates of 2-tetralone with benzyl chloride[2,3]. In these cases, experimental details were lacking as to reaction conditions, isolation procedures, spectral characterization, and yields. Furthermore, the reported physical constants differed so greatly between the two publications as to cast doubt on the authenticity of the product which was isolated. The second procedure consists of reacting 2-hexahydroazepinoindene (**1**, m = 6, n = 1) with benzyl bromide in dioxane/tetrahydrofuran[4]. This enamine alkylation gave a very poor yield (20%) of crude 1-benzyl-2-indanone. Moreover, in this method considerable isolation problems were encountered resulting in a product of poor quality which was not well characterized physically nor spectrally. Surprisingly, this procedure represents the sole example of an alkylation of an enamine derived from 2-indanone or 2-tetralone using a benzyl halide[5]. We report, herein, an improved version of this process.

Our procedure involves the reaction of enamines **1** with a 0.5 molar excess of a benzyl bromide (**2**) in refluxing acetonitrile for 9–24 h. The progress of the reaction is conveniently monitored by I.R. spectroscopy by following the disappearance of the C=C—N absorption at 1565–1575 cm^{-1} and the appearance of the $C{=}N^{\oplus}$ band at 1660–1670 cm^{-1}. Washing of the highly colored crude product **3** with acetone before hydrolysis or recrystallization eliminates entirely the need for tedious column chromatography in the isolation of ketones **4**. Hydrolysis of **3** with aqueous acetic acid/chloroform affords, after recrystallization or distillation, the pure ketones **4** in 57–75% yield.



n = 1,2 m = 4,6
X = Br, J G = H, NO_2

As shown in the Table, this method is far superior to alternative ones employing different solvent systems and conditions. Whereas dioxane has been routinely employed as a solvent for many alkylations[6], we found acetonitrile to be far superior for the alkylation of 2-indanones and 2-tetralones. Thus, we achieved a 57% yield of 1-benzyl-2-indanone using acetonitrile while Blomquist and Moriconi[4] obtained only 20% using dioxane/tetrahydrofuran. Additionally, the ring size

of the amine was of noticeable importance, especially in the alkylation of 2-indanone[4,5]. Finally, the alkylation was facilitated using the more reactive benzyl bromides or iodides rather than benzyl chlorides.

Table. Comparison of Reaction Conditions and Yields in the Preparation of Ketones **4**

Alkylation Product	m	n	X	G	Solvent	Time [h]	Yield [%]
4a	6	1	Br	H	acetonitrile	9	57
	6	1	Br	H	neat	6	23
	6	1	Br	H	dioxane/THF	3.5	20
	6	1	J	H	chloroform	10	0
4b	6	1	Br	NO_2	acetonitrile	24	60
	6	1	Br	NO_2	dioxane	9	20
4c	4	2	Br	H	acetonitrile	15	71
	4	2	J	H	chloroform	12	58
	4	2	Br	H	dioxane	12	0
4d	4	2	Br	NO_2	acetonitrile	14	75
	4	2	Br	NO_2	dioxane	9	52

The structures assigned to products **4** are supported by microanalysis and by I.R. and ^{1}H-N.M.R. spectrometry. The use of the europium shift reagent, Eu(FOD)$_3$, unmasked the ABC pattern in **4a** and allowed for complete interpretation of the spectrum. This complication was not observed in ketones **4b–4d**.

Melting points were obtained with a Thomas-Hoover melting point apparatus and were uncorrected. Distillations were performed on a Büchi-Brinkman Kugelrohrofen micro-distillation oven and boiling points are uncorrected. N.M.R. spectra were recorded on a Hitachi Perkin-Elmer R20-B spectrometer with TMS as an internal standard. I.R. spectra were determined on a Perkin-Elmer model 457 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

1-Benzyl-2-indanone (4a):

1-(1-Benzylindan-2-ylidene)-hexahydroazepinium Bromide (**3a**): A solution of 2-hexahydroazepinoindene[4] (**1**, n = 1, m = 6; 9.1 g, 0.042 mol) and benzyl bromide (10.8 g, 0.063 mol) in acetonitrile (120 ml) is refluxed for 9 h under a nitrogen atmosphere. The dark solution becomes lighter as the alkylation proceeds. Evaporation of the solvent leaves a dark residue which is washed with acetone. Filtration and subsequent acetone wash of the solid affords the iminium salt **3a** as a colorless crystalline solid; yield: 13.9 g (85%); m.p. 210–215°.

I.R. (KBr): ν_{max} = 3008, 2935, 2860, 1670, 1450, 767, 710 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 1.80 (m, 8H, 4 CH$_2$); 3.33 (dd, 2H, J_{vic} = 8 Hz, J_{vic} = 5 Hz, C$\underline{H}_2$—C$_6$H$_5$); 4.20 (m, 6H, 2 CH$_2$—N, CH$_2$—Ar); 5.00 (dd, J_{vic} = 8 Hz, J_{vic} = 5 Hz, CH); 7.15 ppm (m, 9H$_{arom}$).

1-Benzyl-2-indanone (**4a**): The iminium salt **3a** (13.9 g, 0.036 mol) is stirred at room temperature in a mixture of chloroform (10 ml), glacial acetic acid (20 ml), and water (80 ml) for 12 h. Chloroform (75 ml) is added, the organic layer is washed well with water, and dried with magnesium sulfate. The solvent is evaporated and the residue distilled in vacuo to give **4a** as a colorless liquid: yield: 5.3 g (57% based on **1**); b.p. 138–143°/0.05 torr.

I.R. (film): ν_{max} = 3025, 2920, 1750, 1500, 1484, 1460, 1193, 1142, 1076, 750, 698 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 2.94 (dd, 1H, J_{vic} = 8 Hz, J_{gem} = 13.5 Hz, C$\underline{H}_2$—C$_6$H$_5$); 3.28 (dd, 1H, J_{vic} = 5 Hz, J_{gem} = 13.5 Hz, C$\underline{H}_2$—C$_6$H$_5$); 3.30 (s, 2H, CH$_2$—Ar); 3.70 (dd, 1H, J_{vic} = 5 Hz, J_{vic} = 8 Hz, CH); 7.08 ppm (m, 9H$_{arom}$).

^{1}H-N.M.R. [CDCl$_3$ + 0.14 molar Eu(FOD)$_3$]: δ = 2.90 (dd, 1H, J_{vic} = 8 Hz, J_{gem} = 13.5 Hz, C$\underline{H}_2$—C$_6$H$_5$); 3.35 (dd, 1H, J_{vic} = 5 Hz, J_{gem} = 13.5 Hz, C$\underline{H}_2$—C$_6$H$_5$); 3.70 (s, 2H, CH$_2$—Ar); 4.19 (dd, 1H, J_{vic} = 5 Hz, J_{vic} = 8 Hz, CH); 7.08 ppm (m, 9H$_{arom}$).

2,4-Dinitrophenylhydrazone of **4a**: prepared in ethanol and recrystallized from ethyl acetate/ethanol; yellow crystals, m.p. 160–162° (Ref.[4], 230–231°, cf. general text).

$C_{22}H_{18}N_4O_4$	calc.	C 65.66	H 4.51
(402.4)	found	65.57	4.60

1-(4-Nitrobenzyl)-2-indanone (4b):

A solution of 2-hexahydroazepinoindene[4] (2.0 g, 0.009 mol) and 4-nitrobenzyl bromide (3.0 g, 0.014 mol) in acetonitrile (40 ml) is refluxed for 24 h. The procedure described for the preparation of **4a** is then followed and the resultant **4b** recrystallized from ether; yield: 1.5 g (60%); yellow crystals, m.p. 82–84°.

$C_{16}H_{13}NO_3$	calc.	C 71.90	H 4.90
(267.3)	found	72.02	4.96

I.R. (CHCl$_3$): ν_{max} = 3026, 1752, 1610, 1522, 1350, 857 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 3.25 (dd, 2H, J_{vic} = 6 Hz, J_{vic} = 8 Hz, C$\underline{H}_2$—C$_6$H$_5$); 3.38 (s, 2H, CH$_2$—Ar); 3.83 (dd, 1H, J_{vic} = 6 Hz, J_{vic} = 8 Hz, CH); 7.14–7.90 ppm (m, 8H$_{arom}$).

1-Benzyl-2-tetralone (4c):

A solution of 3-pyrrolidino-1,2-dihydronaphthalene[6] (**1**, m = 4, n = 2; 5.0 g, 0.025 mol) and benzyl bromide (6.4 g, 0.04 mol) in acetonitrile (120 ml) is refluxed for 15 h. The procedure described for the preparation of **4a** is then followed and the resultant **4c** distilled in vacuo to give a nearly colorless oil: yield: 4.2 g (71%); b.p. 162–167°/0.05 torr.

I.R. (film): ν_{max} = 3039, 1720, 1500, 1460, 760, 700 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 2.1–2.8 (m, 4H, 2 CH$_2$); 3.15 (d, 2H, J = 7 Hz, C$\underline{H}_2$—C$_6$H$_5$); 3.66 (t, 1H, J = 7 Hz, CH); 7.00 ppm (m, 9H$_{arom}$).

Oxime of **4c**: prepared according to a general procedure[7] and recrystallized from ethanol; m.p. 120–122°.

$C_{17}H_{17}NO$	calc.	C 81.24	H 6.82
(251.3)	found	81.27	6.81

1-(4-Nitrobenzyl)-2-tetralone (4d):

A solution of 3-pyrrolidino-1,2-dihydronaphthalene[6] (5.0 g, 0.025 mol) and 4-nitrobenzyl bromide (8.1 g, 0.04 mol) in acetonitrile (120 ml) is refluxed for 24 h. The procedure described for the preparation of **4a** is then followed and the resultant **4d** recrystallized from chloroform/ether: yield: 5.3 g (75%); yellow crystals, m.p. 108–110°.

$C_{17}H_{15}NO_3$	calc.	C 72.58	H 5.37
(281.3)	found	72.73	5.43

I.R. (CHCl$_3$): ν_{max} = 3030, 1718, 1610, 1522, 1354, 1112, 1018, 854, 691 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$): δ = 2.3–3.0 (m, 4H, 2 CH$_2$); 3.30 (d, 2H, J = 7 Hz, CH$_2$—Ar); 3.80 (t, 1H, J = 7 Hz, CH); 7.05–7.90 ppm (m, 8H$_{arom}$).

The authors gratefully acknowledge support of this investigation by the general research fund of the University of Maine at Orono.

Received: June 4, 1977

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[1] Taken in part from the *Thesis* of D. P. Michaud, University of Maine at Orono, 1977.

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