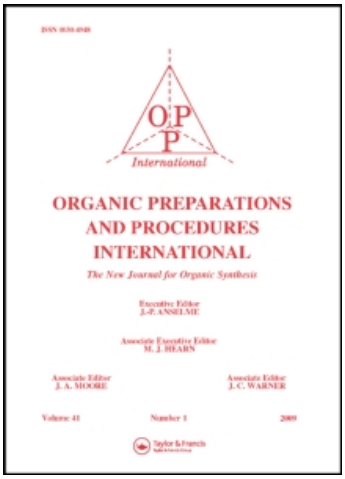


Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

ACYLATION OF 1,2,4,5-TETRAHYDRO-3-MEIHYL-3H-3-BENZAZEPIN-2-ONE IN THE PRESENCE OF SODIUM HYDRIDE

Kazuhiko Orito[a]; Harumi Kaga[b]; Hiroshi Suginome[a]
[a] Department of Chemical Process Ehgineering, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido, JAPAN [b] Government Idustrial Development Laboratory, Hokkaido, Sapporo, Hokkaido, JAPAN

To cite this Article Orito, Kazuhiko , Kaga, Harumi and Suginome, Hiroshi(1989) 'ACYLATION OF 1,2,4,5-TETRAHYDRO-3-MEIHYL-3H-3-BENZAZEPIN-2-ONE IN THE PRESENCE OF SODIUM HYDRIDE', Organic Preparations and Procedures International, 21: 3, 321 — 326
To link to this Article: DOI: 10.1080/00304948909356386
URL: http://dx.doi.org/10.1080/00304948909356386

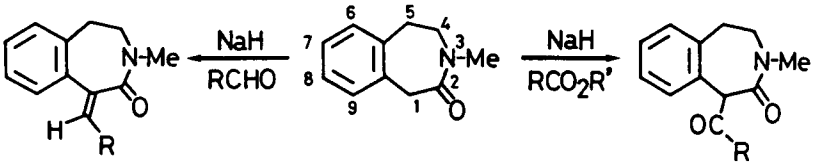
ORGANIC PREPARATIONS AND PROCEDURES INT. 21(3), 321-326 (1989)

ACYLATION OF 1,2,4,5-TETRAHYDRO-3-METHYL-3H-3-BENZAZEPIN-2-ONE IN THE PRESENCE OF SODIUM HYDRIDE†

Kazuhiko Orito*, Harumi Kaga†† and Hiroshi Suginome

Department of Chemical Process Engineering, Faculty of Engineering
Hokkaido University, Sapporo, Hokkaido 060, JAPAN
††Government Industrial Development Laboratory, Hokkaido
Sapporo, Hokkaido 004, JAPAN

Synthetic studies of substituted 3-benzazepines have been achieved by many groups because of a variety of their pharmacological activities[1,2] and also the skeletal features characteristic of isoquinoline alkaloids.[3] In our continuous studies concerning the chemistry of benzolactams, the combination of tetrahydrofuran—N,N-dimethylformamide (THF-DMF) as solvents and sodium hydride (NaH) as base has been shown to work efficiently for C-monoalkylation of 1,2,4,5-tetrahydro-3-methyl-3H-3-benzazepin-2-one.[4] We were also interested in acylation reaction of benzolactams in the presence of NaH, and examined the solvent effects and reactivities to various ester groups in C-acylation of 1.



3 1 2

a) R = C_6H_5
b) R = C_6H_3-3,4-OCH_2O

a) R = C_6H_5
b) R = C_6H_3-3,4-OCH_2O
c) R = C_6H_3-2,3-$(CH_3O)_2$
d) R = C_6H_4-4-Cl
e) R = CHO
f) R = $COCH_3$
g) R = CO_2Et
h) R = $COCO_2Et$

First, the benzazepine 1 was treated with methyl benzoate (1.2 M) and NaH (2 M) in various solvent systems (TABLE I). 1,2-Dimethoxyethane (DME)

and toluene at their boiling point temperature gave 2a in good yields, as shown in TABLE I. Although DMF and dimethylsulfoxide (DMSO) at 120° failed to give 2a, the mixed solvents with THF [THF-DMF (10:1) or THF-DMSO (10:1)] gave 2a in good yields. Increasing the amount of DMF or DMSO to 5:1 improved the yield. THF-DMF (5:1) gave a little better yield than that in DME, but needed the repeated extractions and washes to remove DMF.

TABLE I. Reaction of Benzolactam 1 with Methyl Benzoate[a]

Solvent/bath temp.	Yield[b]	Solvent/bath temp.	Yield[b]
THF/85°	14%	DMSO/120°	<2%
benzene/99°	0%	THF-DMF(10:1)/85°	74%
toluene/127°	63%	THF-DMF(5:1)/85°	86%
dioxane/115°	16%	THF-DMSO(10:1)/85°	67%
DME/100°	84%	THF-DMSO(5:1)/85°	86%
DMF/120°	<1%		

a) Methyl benzoate (1.2 eq.), NaH (2 eq.) and 1 mmole of 1.
b) 2a/1+2a, averages of two or three runs.

Thus, the reaction of 1 with the appropriate ester (1.2 M) in the presence of NaH (2 M) was attempted in gently boiling DME for the times specified in TABLE II. The crude products, obtained from the reactions with the methyl benzoates, were found to be the keto-enol mixtures by their ^1H NMR spectra, which revealed two singlet peaks in almost 1:1 near at δ 10.5 and 5.6 due to the enol-OH and C_1-H. Treatment of these mixtures on silica gel TLC brought about the isomerization to the ketones (2a-d, 84-96%). No reaction took place between 1 and methyl 4-nitrobenzoate or methyl nicotinate, and 1 was quantitatively recovered. In the similar way, ethyl formate could give 2e (27%). Ethyl esters of acetic, propionic, butyric, isobutyric and valeric acid gave the intractable mixtures containing the unchanged starting azepine, self-condensed products of the reagent esters and compounds formed by further condensation of primary products. Substitution of t-butyl acetate for ethyl acetate resulted in the good

formation of the 1-acetyl-3-benzazepinone (2f). However, other ^{t}butyl esters turned out to be not practically good acylating reagents in DME or THF-DMF or toluene. Neither 2f nor 2a was obtained from the acylation reaction using the corresponding acid chlorides or anhydrides. The reactions with diethyl carbonate and diethyl oxalate proceeded smoothly to give 2g (85%) and 2h (90 %). 2h was isolated as a 6:5 mixture of the keto and enol forms.

TABLE II. Reaction of 1 with Various Carbonyl Compounds in DME

Entry	Reaction time (hr)	Products 2 and 3	
		yield(%)	mp.(°C)(solvent)
2a: $C_6H_5CO_2Me$	4.0	90	180-187(acetone)
2b: 3,4-OCH_2O-$C_6H_3CO_2Me$	4.0	87	163-164(acetone)
2c: 2,3-$(CH_3O)_2C_6H_3CO_2Me$	8.5	84	130-132(acetone)
2d: 4-$ClC_6H_4CO_2Me$	6.0	96	157-160(acetone)
2e: HCO_2Et	2.5	27	thick oil
2f: $CH_3CO_2{}^{t}Bu$	5.5	85	106-108(benzene-ether)
2g: $CO(OEt)_2$	4.0	87	174-176(AcOEt)
2h: $(CO_2Et)_2$	0.5	90	106-107(ether)
3a: C_6H_5CHO	4.0	37	146-147(acetone-ether)
3b: 3,4-OCH_2O-C_6H_3CHO	8.0	30	162-163(acetone-ether)

In addition, the reaction of 1 with an aldehyde was also attempted using benzaldehyde and 3,4-methylenedioxybenzaldehyde. The products (3a,b) were assigned to have the benzylidene double bond cis to the amide group, since in ^{1}H NMR analysis of 3b irradiation of the olefinic proton signal at δ 6.55 caused Nuclear Overhouser enhancement at the signal due to C_9-H (δ 7.40 as well as $C_{2'}$-H (δ 7.10) and $C_{6'}$-H (δ 6.98). Main by-products were the corresponding benzyl alcohols formed by the competitive Cannizzaro reaction. Michael type addition of 1 to methyl acrylate, methyl cinnamate[5] and β-nitrostylene failed.[6]

EXPERIMENTAL SECTION

THF, benzene, toluene, DME and dioxane were dried over sodium through reflux. DMF and DMSO were treated with P_2O_5 and CaH_2, respectively, and distilled under reduced pressure before use. IR spectra were obtained as nujol mulls on a Hitachi Perkin-Elmer Model 125 spectrophotometer, unless otherwise noted. UV spectra were recorded a Hitachi 124 spectrophotometer. ^{1}H NMR spectra were determined in $CDCl_3$ solution with Me_4Si as internal standard (δ=0) on a 90 MHz Hitchi R-22[3] spectrometer, and [4]the irradiation study was carried out on a Bruker MSL 400 spectrometer. High resolution mass spectral analysis (HR-MS) was obtained on a JEOL JMS D300 spectrometer at 70 eV under electron impact condition. Melting points were taken on a Laboratory Devices MEL-TEMP and are uncorrected. Preparative TLC was run on Merck Kieselgel 60 PF_{254} (No. 7749).

Reaction of 1,2,4,5-Tetrahydro-3-methyl-3H-3-benzazepin-2-one (1) with Esters or Aromatic Aldehydes.- A stirred suspension of 3-methyl-1,2,4,5-tetrahydro-3H-3-benzazepin-2-one[4] (1) (175 mg, 1 mmol), the appropriate ester or aldehyde (1.2 mmol) and sodium hydride (96 mg containing 50% oil, 2 mmol) in dry solvent (2 ml) was heated to gentle reflux under an atmosphere of nitrogen for the appropriate number of hours in TABLE II. The mixture was evaporated at room temperature, diluted with water (10 ml), acidified with 0.5N HCl to pH 5, and extracted with CH_2Cl_2 (5 ml × 2, or × 5 times for the reaction using DMF or DMSO). The extracts were washed with water (10 ml × 1, or 5), dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was crystallized from the appropriate solvent (Table II), or purified by silica gel TLC developing with 1-3% MeOH-CH_2Cl_2 and extracting with MeOH-CH_2Cl_2 (1:2).

2a: IR: 1675, 1650, 1595, 1583 cm^{-1}; ^{1}H NMR: δ 2.97 (3H, s, NCH_3), 3.0-3.3 (3H, m, C_5-H_2 and C_4-H), 3.7-4.3 (1H, m, C_4-H), 5.60 (1H, s, C_1-H), 6.9-7.3 (4H, m, $C_{6,7,8,9}$-H), 7.3-7.7 (3H, m, $C_{3',4',5'}$-H), 8.1-8.3 (2H, m, $C_{2',6'}$-H).

Anal. Calcd for $C_{18}H_{17}NO_2$; C, 77.39; H, 6.13; N, 5.01
Found; C, 77.46; H, 6.27; N, 5.14

2b: 1660, 1645, 1603, 1580 cm^{-1}; δ 2.99 (3H, s, NCH_3), 3.0-3.3 (3H, m, C_5-H_2 and C_4-H), 3.7-4.3 (1H, m, C_4-H), 5.52 (1H, s, C_1-H), 6.04 (2H, s,

OCH_2O), 6.87 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.9-7.3 (4H, m, $C_{6,7,8,9}$-H), 7.63 (1H, d, J=1.8 Hz, $C_{2'}$-H), 7.97 (1H, dd, J=8.1, 1.8 Hz, $C_{6'}$-H).

Anal. Calcd for $C_{19}H_{17}NO_4$; C, 70.57; H, 5.30; N, 4.33

Found; C, 70.34; H, 5.17; N, 4.25

2c: 1700, 1645, 1580 cm^{-1}; δ 2.96 (3H, s, NCH_3), 2.8-3.4 (3H, m, C_5-H_2 and C_4-H), 3.7-4.2 (1H, m, C_4-H), 3.85, 3.90 (each 3H, s, 2 CH_3O), 5.52 (1H, s, C_1-H), 6.8-7.2 (7H, m, Ar-Hs).

Anal. Calcd for $C_{20}H_{21}NO_4$; C, 70.78; H, 6.24; N, 4.13

Found; C, 70.93; H, 6.21; N, 4.13

2d: 1680, 1645, 1600, 1578 cm^{-1}; δ 2.98 (3H, s, NCH_3), 2.9-3.2 (3H, m, C_5-H_2 and C_4-H)), 3.7-4.2 (1H, m, C_4-H), 5.55 (1H, s, C_1-H), 6.9-7.3, (4H, m, $C_{6,7,8,9}$-H), 7.44, 8.16 (each 2H, AB type J=8.7 Hz, $C_{3',5'}$- and $C_{2',6'}$-H).

Anal. Calcd for $C_{18}H_{16}NO_2Cl$; C, 68.88; H, 5.14; N, 4.46; Cl, 11.30

Found; C, 69.01; H, 5.23; N, 4.55; Cl, 11.26

2e: (neat) 2900-2200, 1695, 1635, 1600, 1575 cm^{-1}; δ 2.99 (3H, s, NCH_3), 2.95-3.20 (2H, m, C_5-H), 3.45-3.70 (2H, m, C_4-H), 6.95-8.30 (4H, m, $C_{6,7,8,9}$-H), 7.37 (1H, d, J=10.1 Hz, C_1-H), 14.93 (1H, d, J=10.1 Hz, CHO). HR-MS, m/z 203.0952 ($C_{12}H_{13}O_2N$ requires 203.0946).

2f: 1715, 1640 cm^{-1}; δ 2.19 (3H, s, $COCH_3$), 2.9-3.9 (4H, m, $C_{5,4}$-H), 3.05 (3H, s, NCH_3), 4.75 (1H, s, C_1-H), 6.9-7.3 (4H, m, $C_{6,7,8,9}$-H).

Anal. Calcd for $C_{13}H_{15}NO_2$; C, 71.86; H, 6.96; N, 6.45

Found; C, 71.81; H, 6.89; N, 6.41

2g: 1732, 1660 cm^{-1}; δ 1.26 (3H, t, J=7.3 Hz, CH_3CH_2), 3.06 (3H, s, NCH_3), 3.0-4.1 (4H, m, $C_{5,4}$-H), 4.23 (2H, q, J=7.3 Hz, CH_3CH_2), 4.78 (1H, s, C_1-H), 7.19 (4H, br s, $C_{6,7,8,9}$-H).

Anal. Calcd for $C_{14}H_{17}NO_3$; C, 67.99; H, 6.93; N, 5.66

Found; C, 67.88; H, 6.67; N, 5.49

2h: 3100, 1715, 1645, 1620 cm^{-1}; 6:5 intensities of keto form [δ 1.35 (3H, t, J=7.0 Hz, CH_3CH_2), 3.07 (3H, s, NCH_3), 2.9-3.3, 3.3-3.7 (each 2H, m,

$C_{5,4}$-H), 4.37 (2H, q, J=7.0 Hz, $C\underline{H}_3CH_2$), 6.06 (1H, s, C_1-H), 6.9-7.35 (4H, m, $C_{6,7,8,9}$- H)] and enol form [δ 0.95 (3H, t, J=7.0 Hz, $C\underline{H}_3CH_2$), 2.97 (3H, s, NCH_3), 2.95-3.3, 3.3-3.65 (each 2H, m, $C_{5,4}$-H), 4.00 (2H, q, J=7.0 Hz, $CH_3C\underline{H}_2$), 6.9-7.35 (4H, m, $C_{6,7,8,9}$-H), 14.61 (1H, br s, enol OH)].

Anal. Calcd for $C_{15}H_{17}NO_4$; C, 65.44; H, 6.22; N, 5.09

Found; C, 65.19; H, 6.27; N, 4.92

3a: 1640, 1600, 1570 cm^{-1}; UV λ_{max}(MeOH) 274 nm (ε 22,600); δ 3.15 (3H, s, NCH_3), 3.0-3.25 (4H, m, $C_{5,4}$-H), 6.65 (1H, s, olefinic H), 7.0-7.6 (9H, m, Ar-H).

Anal. Calcd for $C_{18}H_{17}NO$; C, 82.10; H, 6.51; N, 5.32

Found; C, 82.01; H, 6.72; N, 5.33

3b: 1640, 1600, 1580 cm^{-1}; λ_{max}(MeOH) 311 nm (ε 15,500) and 284 nm (ε 13,300); δ 3.0-3.25, (4H, m, $C_{5,4}$-H), 3.14 (3H, s, NCH_3), 5.95 (2H, s, OCH_2O), 6.55 (1H, s, olefinic H), 6.76 (1H, d, J=8.1 Hz, $C_{5'}$-H), 6.98 (1H, dd, J= 8.1, 1.5 Hz, $C_{6'}$-H), 7.10 (1H, d, J= 1.5 Hz, $C_{2'}$-H), 7.1-7.3 (3H, m, $C_{6,7,8}$-H), 7.35-7.45 (1H, m, C_9-H).

Anal. Calcd for $C_{19}H_{17}NO_3$; C, 74.25; H, 5.58; N, 4.56

Found; C, 74.31; H, 5.47; N, 4.48

REFERENCES

† Benzolactams-III, For Part II, see K. Orito, H. Kaga, M. Itoh, S. O. de Silva, R. H. Manske and R. Rodrigo, J. Heterocycl. Chem., 17,417 (1980).

1. S. Kasparek, "Advances in Heyerocyclic Chemistry", Vol. 17, Ed. by A. R. Katritzky and A. J. Boulton, Academic Press, New York, 1974, p. 98.
2. B. Pecherer, R. C. Sunbury and A. Brossi, J. Heterocycl. Chem., 9, 609 (1972).
3. T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Hirokawa, Tokyo and Elsevier, Amsterdam (1968).
4. K. Orito and T. Matsuzaki, Tetrahedron, 36, 1017 (1980)
5. R. B. Meyer and C. R. Hauser, J. Org. Chem., 26, 3187 (1961).
6. V. Ehrig and D. Seebach, Chem. Ber., 100, 1961 (1975).

(Received November 28, 1988; in revised form March 3, 1989)