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Synthetic Studies of Heterocyclic Compounds I

Alkylation and Acylation of 1, 2, 4, 5-Tetrahydro-3-methyl-3H-3-benzazepin-2-one

Kazuhiko ORITO* and Tsutomu MATSUZAKI*

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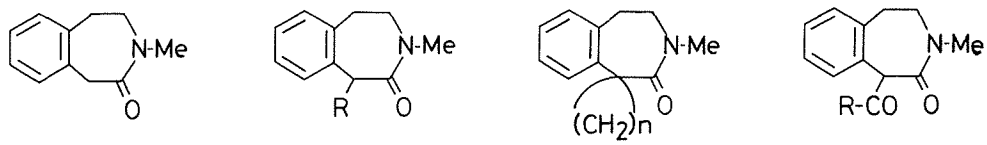
Abstract

Alkylation of the title azepinone 1 with alkyl halides was studied using a combination of sodium hydride and tetrahydrofuran-N, N-dimethylformamide solvent system. This resulted in the efficient formation of monoalkyl derivatives 2 as well as spiro compounds 3. Ester condensation type reaction of 1 was also achieved to give 1-acylbenzazepinones 4.

Introduction

As a result of current interest in pharmacological activities[1,2] and also as a skeletal feature of some isoquinoline alkaloids[3], several methods for the preparation of substituted or unsubstituted 3-benzazepines have been reported[1]. Exploitation of efficient prepanation of substituted 3-benzazepinones, as possible 3-benzazepine equivalents, should be an alternative approach to the above subject. However, systematic studies on the introduction of substituents on the azepinone ring system of 3-benzazepinones are not available in the liserature. Thus, we intended to devise possible methods in practical and convenient functionalization of 3-benzazepinones.



1 2 3 a. n=4 b. n=5 4

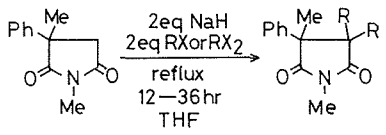
Fig. 1

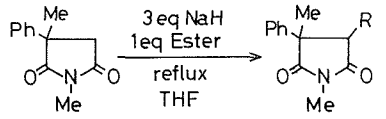
Results and Discussion

The α-functionalization of amide groups has been employed generally using strong base, such as sodium or potassium amide, dialkylamide lithium, or butyl lithium[4], proceeding *via* a suitable trapping of generated carbanion intermediates. On the contrary, examples using sodium hydride, despite its experimental ease, have been less often reported, especially with the definite lack of the systematic studies for cyclic carboxamides, the so-called lactams. The figures depicted below

* Department of Chemical Process Engineering, Faculty of Engineering, Hokkaido University

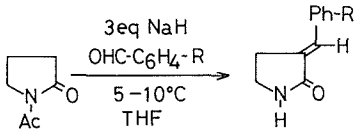
by Hauck and Fan





entry	product R:	yield
MeI	Me–)2	26 %
iso-PrBr	iso-Pr–, H–	10 %
CH_2=$CHCH_2$Br	CH_2=$CHCH_2$–)2	46 %
Br(CH_2)4Br	–(CH_2)4–	56 %
Br(CH_2)5Br	–(CH_2)5–	82 %
CO(OEt)2	EtOOC–	90 %
HCOOEt	OHC–	75 %
CH_3COOEt	CH_3OC–	80 %
(COOEt)2	EtOOCOC–	66 %
C_6H_5COOEt	C_6H_5CO–	62 %

by Zimmer et al.



product R:	yield
H	68 %
2-OMe	54 %
4-OMe	30 %
3,4-OCH_2O–	66 %
3,4-(OMe)2	45 %
2,4,6-(OMe)3	79 %

Fig. 2

indicate Hauck or Zimmer's results of the reactions of cyclic imides with sodium hydride in tetrahydrofuran selected as a solvent by both groups. Hauck et al.[5] described the method for the alkylation and acylation of N-methylsuccinimide, in which monoalkyl derivatives were obtained in a low yield. However, the acylation by the ester-condensation reaction furnished the corresponding acyl derivatives in good yields. Zimmer[6] prepared various benzylidene derivatives of 2-pyrrolidinone from N-acetyl-2-pyrrolidinone. On the formation of carbanion prior to the α-functionalization lactam may be considered to be less reactive than the corresponding cyclic imide, because the latter nitrogen atom is less basic due to the electron withdrawing effect of the second carbonyl group. Therefore, lactam, even the benzolactam **1**, may need a more effective condition.

The new azepinone **1**, mp 114.5–116.5°C, which was taken up as a simplest model possibly employed in the present operation, was easily prepared by heating N-chloroacetyl-N-methylphenethylamine with anhydrous aluminum chloride in 70% yield, in accordance with Nair and Malik's psocedure[7]. Alkylation was carried out by heating the stirred suspension of **1** and given amounts of sodium hydride and appropriate halides in a mixture of dry tetrahydrofuran and N, N-dimethylformamide (10 : 1 volume %)[8] under the conditions specified in Table 1. This solvent system was selected in the hope that the addition of N, N-dimethylformamide to tetrahydrofuran could increase the metalation ability of NaH and a large ratio of tetrahydrofuran to N, N-dimethylformamide could decrease the tar formation due to the side reaction of halides as well as the compounds. In fact, the reaction of **1** with n-butyl bromide in this solvent system proceeded smoothly to give the monobutyl derivative **2** (isolated yield, 93%) as shown in the Table 1. Replacement of this solvent system to the commonly used solvents, tetrahydrofuran, dioxane, dimethoxyethane, benzene and toluene, caused slower alkylation reactions by a factor of 2–70 times, respectively. This observation is

Table 1. Alkylation and Acylation of 1, 2, 4, 5-Tetrahydro-3-methyl-3H-3-benzazepin-2-one **1**

Halide or Ester (equiv)	NaH (equiv)	Bath Temp. /°C	Reaction Time/hr	Product	/%	M. p. or B. p. (mmHg)/°C
MeI (3.0)	2	50	2.5	**2a**	85	75–77
n-PrBr (1.1)	2	80	3.0	**2b**	91	131–132 (0.08)
n-BuBr (1.1)	2	80	3.0	**2c**	93	147–149 (0.2)
iso-BuBr (1.1)	2	80	3.0	**2d**	86	141–142 (0.09)
n-Hexyl Br (1.1)	2	80	3.0	**2e**	82	190–192 (0.5)
allyl Br (1.1)	2	80	2.0	**2f**	89	190–191 (0.5)
$PhCH_2Br$ (1.1)	2	80	2.0	**2g**	85	128–129.5 (Benzene-Ether)
3, 4-$OCH_2OC_6H_3CH_2Br$ (1.1)	2	80	3.0	**2h**	81	124–126 (Ether)
2. 3-$(MeO)_2C_6H_3CH_2Br$ (1.1)	2	80	3.0	**2i**	91	144–145.5 (Ether)
iso-PrBr (1.1)	2	80	2.0	**2j**	63	123–124 (0.09)
cyclohexyl Br (1.1)	2	80	2.0	**2k**	44	157–159 (0.09)
$Br(CH_2)_3Br$ (1.1)	2	80	2.0	**2f**	80	190–191 (0.5)
$Br(CH_2)_4Br$ (1.1)	3	80	4.0	**3a**	63	61–62 (Bgnzene-Ether)
$Br(CH_2)_5Br$ (1.1)	3	80	4.0	**3b**	42	103–104 (Benzene-Ether)
C_6H_5COOMe (1.2)	3	100	4.0	**4a**	90	185–187 (acetone)
3, 4-$OCH_2OC_6H_3COOMe$(1.2)	2	100	4.0	**4b**	87	163–164 (acetone)
2, 3-$(MeO)_2C_6H_3COOMe$ (1.2)	2	100	8.5	**4c**	84	139.5–141.5 (acetone)
$CO(OEt)_2$ (1.2)	2	100	4.0	**4d**	87	106.5–107 (Ether)
$(COOEt)_2$ (1.2)	2	100	0.5	**4e**	90	174–176 (EtOAc)

found to be in good agreement with the above expectation. Going back to the tetrahydrofuran-N, N-dimethylformamide system, alkylation with a variety of halides was examined. Primary halides gave the corresponding alkyl, allyl and benzyl derivatives **2** in satisfactory yields, even in case of bulky isobutyl bromide, and secondary halides resulted in lower yields than primary halides. Excess halides do not tend to cause dialkylation, but promotes monoalkylation[9]. Attempted experiments using the mono-n-butylbenzazepinone **1** and each 1.0 mole equiv of NaH and n-butyl bromide for 1.5 hr revealed less ability of this solvent system for dialkylation of **1** into the mole ratio 0.09 of the produced di-n-butyl derivative[10] to the unchanged **1** (0.20 for boiling toluene and 0.59 for boiling dioxane). It is, however, noteworthy that **1** was readily dialkylated with 1, 4-dibromobutane or 1, 5-dibromopentane to afford the corresponding 5- or 6-membered spiro compound **3**, respectively, since toluene and dioxane produced only small amounts of **3** accompanied with oily by-products. 1, 2-Dibromoethane and 1, 3-dibromopropane failed to give the corresponding spiro compounds, and the latter bromide yielded **2f** instead in 80% yield, which had been already obtained by the interaction with allyl halide. Attempted reaction with benzaldehyde or benzophenone in this solvent system to produce benzylidene type compound such as Zimmer's products gave only a starting material **1**, contrary to their results[6]. Acylation was first attempted by benzoylation with methylbenzoate in the above tetrahydrofuran-N, N-dimethylformamide solvent system and resulted in the recovery of most of the starting material **1**. The change of the solvent system to dimethoxyethane gave satisfactory results even in the production of alkoxybenzoyl derivatives **4b, c.** The pmr analysis showed that all three crude products isolated were in mixtures of keto- and enol-forms (about 1:2). The ketones were isolable in pure state on fractional crystallization from acetone, and also might be obtained

by the certain treatment effecting the equilibrium of this fraction to the one end, hopefully to the ketone. In fact, when a tautomeric mixture of **4a** was subjected to the preparative thin layer chromatography on an activated silica gel, developed with methylene chloride, quantitative recovery of **4a** in the pure keto-form was successful. As shown in reaction times (4 hr for **4b** and 8.5 hr for **4c**) in the Table 1, *ortho*-alkoxybenzoate reacted at a slower rate than the others, while this effect was not clearly observed in the benzylation using the corresponding benzyl bromides as described above. Similarly, dimethyl carbonate and diethyl oxalate gave **4d** and **4e** in good yields.

Thus, sodium hydride combined with tetrahydrofuran-N, N-dimethylformamide offers efficient monoalkylation and spiro ring formation on 3-benzazepin-2-ones, and also the ester condensation reaction of **1** was found to proceed readily with sodium hydride. It seems to be reasonable that this procedure may also be applicable not only to certain substituted 3-benzazepines but also to other benzolactams.

References and Notes

1) Substituted 3-benzazepines were found to have analgesic, anolectic, anorexigenic, depressant, hypotensive, hypoglcemic, antidiabetic, antibacterial, antidepressant, antihypertensive, ganglion blocking activities and so on; S. Kasparek: *Advances in Heterocyclic Chemistry*, Vol. 17, Edited by A. J. Katritzky and A. J. Boulton; Academic Press, New York, N. Y., 1974, P. 45.
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3) 3-Benzazepine skeleton is found in the rhoeadine, isopavine and cephalotaxine alkaloids; T. Kametani: *The Chemistry of the Isoquinoline Alkaloids*, Hirokawa Publishing Company, Inc., Tokyo, and Elsevier Publishing Company, Amsterdam, 1968; T. Kametani: *The Chemistry of the Isoquinoline Alkaloids*, Vol. 2, The Sendai Institute of Heterocyclic Chemistry, Sendai, Japan, 1974; M. Shamma: *The Isoquinoline Alakloids*, Academic Press, New York, N. Y., 1972.
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5) F. P. Hauck, Jr. and J. T. Fan: *J. Org. Chem.*, 34, 1703 (1969).
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7) M. D. Nair and P. A. Malik: *Indian J. Chem.*, 5, 169 (1967).
8) This solvent system has been successfully used in N-methylation of amide groups; J. R. Coggins and N. L. Benoiton: *Can J. Chem.*, 49, 1968 (1971); K. Orito, R. H. Manske and R. Rodrigo: *J. Am. Chem. Soc.*, 96, 1944 (1974).
9) 1, after heating with each 2 mole equiv of n-butyl bromide and NaH for 2 hr, gave the mono-n-butyl derivative **2c** in the comparable yield (89%).
10) Dibutylbenzazepinone, bp 137-139°C/0.1 mmHg, was prepared with a large excess of NaH and n-butyl bromide in dioxane in another run, and served as an authentic sample.