SYNTHESIS OF 1,2,3,4-TETRAHYDRO-1-BENZAZOCIN-5(6H)-ONES BY DIECKMANN CONDENSATION

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Abstract----Tetrahydro-1-benzazocin-5(6H)-ones (5,6,8-10) have been conveniently prepared by the Dieckmann condensation of the diester 1 and 3, or the ester nitrile 4 by using sodium-potassium alloy as an effective base.

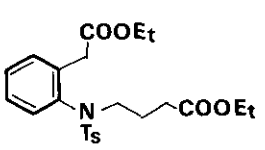
1,2,3,4-Tetrahydro-1-benzazocin-5(6H)-ones are attractive intermediates for the synthesis of pyrrolo[1,2-a]indole framework of mitomycins.[1] Reasonable and easy access to the nitrogen-containing eight-membered ring ketones seems to rely on Dieckmann condensation. It was Procter et al.[2] who first applied the methodology on the diester 1 by using tert-BuOK or NaH as a catalyst, but failed to induce the desired cyclization. Later, Lown and Itoh[3] reported successful cyclization of the closely related diester 2 in the presence of tert-BuOK, though the product yield was less than 32% even under carefully controlled reaction conditions. We have recently reinvestigated the Dieckmann condensation of 1 and related coupounds (3 and 4), and established the procedure effecting the reaction to proceed in preparatively acceptable yields as described below.

When the diester 1 was treated with tert-BuOK in refluxing benzene or toluene for several hours under high-dilution condition, the corresponding dicarboxylic acid was the only product isolated in 57% yield after usual workup. Switching the alkoxide to Na-K alloy, however, the ester condensation proceeded nicely to produce a mixture of the isomeric keto esters 5 and 6, which were isolated by silica gel chromatography in 29% and 30% yields respectively. These compounds were readily transformed to N-p-toluenesulfonyl-1,2,3,4-tetrahydro-1-benzazocin-5(6H)-one (7) by heating with sulfuric acid in tetrahydrofuran: 73% yield for 5 (7 hr) and 60% yield for 6 (4 days).

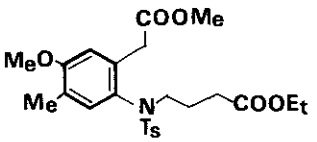
With the successful result on Dieckmann azocinone annulation to 1, we next applied the procedure to benzylic α-methyl esters 3 and 4 which were prepared from 3-methyl-2-indolinone.[4] As shown in the

Table I, improvement in the yields of benzazocinones by use of Na-K is remarkable when compared with the runs employing conventional reagents such as NaH or tert-BuOK. In the case of 4, Na alone afforded slightly better yield in one experiment, but we recommend the combination with K for obtaining reproducible result. The β-keto esters 8 and 9 obtained here were subjected to dealkoxycarbonylation with 20% sulfuric acid in tetrahydrofuran under reflux to give 11 in good yield.

Experiments aimed at the synthesis of modified mitomycin structures using the compounds reported here are in progress. All new compounds appeared in this paper were characterized by spectral data and elemental analyses which were summarized in Table II.



1



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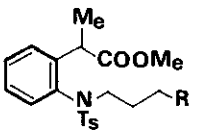
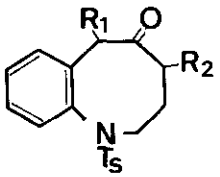


3 : R = COOEt
4 : R = CN



	R_1	R_2
5 :	H	COOEt
6 :	COOEt	H
7 :	H	H

	R_1	R_2
8 :	Me	COOMe
9 :	Me	COOEt
10 :	Me	CN
11 :	Me	H

Table I. Dieckmann Cyclization of 1, 3, and 4.

Substrate	Base	Reaction Time (hr)[a]	Yield of Benzazocinone
1	Na-K	6	5 (29%), 6 (30%).
3	NaH[b]	10	9 (4%).
	t-BuOK[b]	9	9 (5%).
	Na	4.5	8 (20%), 9 (44%).
	Na-K	2	8 (26%), 9 (29%).
4	NaH[b]	20	10 (5%).
	Na	5	10 (27%).
	Na-K	5	10 (46%).

a) in refluxing toluene. b) high-dilution method.

Dieckmann condensation of 3:

Metallic sodium (1.50 g, 6.52 mg atom) and potassium (0.5 g, 13.6 mg atom) in dry toluene (180 ml) under nitrogen atmosphere were heated at reflux and dispersed with vigorous stirring. A solution of 3 (6.11 g, 15.2 mmol) in dry toluene (22 ml) was added, and the mixture was gently refluxed with stirring for 4 h. After the reaction mixture being cooled, the reaction mixture was quenched by addition of acetic acid (9 ml) and methanol (if undestroyed metal is observed), and water was added to separate organic layer. The aqueous layer was extracted with benzene. The organic layers were combined, washed with brine, and dried over magnesium sulfate. After removal of the solvent at reduced pressure, the residue was subjected to a column chromatography (silica gel, 250 g). Elution with hexane-ethyl acetate afforded 9 (1.59 g, 29%) and then 8 (1.43 g, 26%). The analytical samples were obtained by recrystallization from isopropyl ether.

Table II. Physical and Spectral Data of Tetrahydro-1-benzazocin-5(6H)-ones

Compound[a]	mp(°C)	IR(KBr) cm^{-1}	NMR($CDCl_3$, 60 MHz), δ
5	148-149	1740 1705	1.20(3H,t, J=7Hz,CH_3-CH_2),1.67-2.40(2H,m,-CH_2-),2.43(3H,s,CH_3-Ar), 3.40-4.33(5H,m),3.90(2H,br s,CO-CH_2-Ar).
6	152-154	1640 1610	1.23(3H,t, J=7Hz,CH_3-CH_2),1.50-2.40(4H,m,CH_2-CH_2-CO),2.43(3H,s, CH_3-Ar),2.53-3.23(1H,m,-CH-N),3.86-4.60(3H,m,CH_2-O, -CH-N), 12.83(1H,s,C=C-OH).
7	162-163	1700	1.67-2.16(2H,br m,-CH_2-),2.23-2.41(2H.br m,-CH_2-CO),2.43(3H,s, CH_3-Ar),3.10-4.16(2H,br m,-CH_2-N),3.80(2H,br s,-CO-CH_2-Ar).
8	142-145	1740 1700	1.60(3H,d, J=7Hz,CH_3-CH-CO),1.50-2.60(2H,m,-CH_2-),2.50(3H,s,CH_3-Ar), 2.60-4.45(3H,m,-CH_2-N, CO-CH-COO),3.65(3H,s,CH_3-O),3.88(1H,q, J=7Hz, CH_3-CH-CO).
9	146-149	1730 1700	1.20(3H,t, J=7Hz,CH_3-CH_2-O),1.60(3H,d, J=6.5Hz,CH_3-CH-CO),1.50- 2.30(2H,m,-CH_2-),2.60-3.60(3H,m,-CH_2-N, CO-CH-COO),3.85(1H,q, J= 6.5Hz,CH_3-CH-CO),4.13(2H,q, J=7Hz,CH_3-CH_2-O).
10	177-179	2270 1720	1.61(3H,d, J=7Hz,CH_3-CH),1.53-2.25(2H,m,-CH_2-),2.66-3.90(3H,m, -CH_2-N, -CH-CN).
11	155-157	1700	1.43 and 1.57(3H(1:1),d(each), J=7Hz,CH_3-CH-CO),1.70-2.60(4H,m, -CH_2-CH_2-CO),2.40(3H,s,CH_3-Ar),2.65-3.00 and 3.00-3.30(1H(1:1), -CH-N),3.70-4.00 and 4.00-4.30(1H(1:1),-CH-N),3.60 and 4.50(1H (1:1),q-like(each), J=7Hz,CH_3-CH-CO).

a) The microanalyses were in good agreement with the calculated values within C, ± 0.27, H, ± 0.21, and N, ± 0.23.

REFERENCES AND NOTES

1. For a review: T.Kametani and K.Takahashi, Heterocycles, 1978, 9, 293.

2. G.R.Proctor and W.I.Ross, J. Chem. Soc., Perkin Trans. I, 1972, 886.

3. J.W.Lown and T.Itoh, Can. J. Chem., 1975, 53, 960.

T.Itoh, T. Hata, and J.W. Lown, Heterocycles, 1976, 4, 47.

4. The following sequence of reactions was employed: i) hydrolysis by heating with an excess amount of barium hydroxide, ii) N-tosylation, iii) esterification with methanolic hydrogen chloride (an overall yield of methyl 2-(2-p-toluenesulfonylamidophenyl)propionate, 42%. mp 88-89°C), iv) N-alkylation with ethyl 4-bromobutyrate or 4-bromobutyronitrile in refluxing acetone in the presence of potassium carbonate to give 3 (95%) or 4 (72%).

3: mp 69-70°C. IR(KBr) cm^{-1} : 1735. NMR($CDCl_3$) δ : 1.20 (3H,t, J=7Hz, CH_3-CH_2),1.54 (3H,d, J=7Hz, CH_3-CH),1.76 (2H,m, -CH_2-),2.32 (2H,t, J=7Hz, -CH_2-CO), 2.44 (3H,s, CH_3-Ar),3.26 (1H,m, -CH-N), 3.62 (3H,s, CH_3-O), 3.84 (1H,m, -CH-N), 4.10 (2H,q, J=7Hz, -CH_2-CH_3), 4.47 (1H,q, J=7Hz, CH_3-CH-).

4: mp 122-124°C. IR(KBr) cm^{-1}: 2250, 1735. NMR($CDCl_3$) δ : 1.55 (3H,d, J=7Hz, CH_3-CH-), 1.88 (2H,m, -CH_2-), 2.45 (3H,s, CH_3-Ar), 2.61 (2H,m, -CH_2-CN),3.50 (2H,m, -CH_2-N), 3.67 (3H,s, CH_3-O), 4.42 (1H,q, J=7Hz, -CH-CH_3).

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