APPLICATION OF MAGNESIUM ALKOXIDES TO SYNTHESES OF BENZOHETEROCYCLIC COMPOUNDS

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The Dieckmann condensations of methyl [(2-methoxycarbonyl)phenyl]-X-acetates *Ia – Ih* (X = O, S, SO_2, NH, NCH_3) initiated by action of magnesium methoxide, ethoxide, isopropoxide and other basic reagents have been studied under various conditions. Whereas magnesium methoxide has comparable efficiency as sodium methoxide and potassium tert-butoxide in syntheses of the benzoheterocyclic compounds *IIa – IIh*, magnesium ethoxide gives the ethyl ester *IIb* in a medium yield, and magnesium isopropoxide is quite inefficient in the condensation reaction. The alkylation of the esters *IIa*, *IId*, and *IIg* with methyl chloroacetate in the presence of sodium hydride in dimethylformamide gives the diesters *IIi – IIk* which on action by potassium tert-butoxide undergo the cyclization reaction to give esters *III*.

The Dieckmann condensations[1] of diesters of carboxylic acids have found broad applications in syntheses of various benzoheterocyclic compounds[2 – 13]. The basic condensation reagents useful in these syntheses include alkali metals in aromatic hydrocarbon media, alkali carbonates and hydroxides, and especially alkali alkoxides in corresponding alcohols; some data[10], however, are only of qualitative nature. The application of magnesium alkoxides is sporadic in the Dieckmann type condensations[14,15], and a successful application of magnesium methoxide is described in a patent[16]. However, magnesium methoxide was successful in some regioselective aldolization reactions[17 – 19] due to the chelatation ability of the magnesium(II) ion. With regard to these facts, we decided to verify the reactivity of magnesium alkoxides as compared with that of other bases in the Dieckmann condensation of the diesters *Ia*, *Id – Ih* giving the benzoheterocyclic products of the types *II* and *III*. The compounds of this type represent important synthons in syntheses of biologically active compounds[20 – 22].

The easily accessible methyl [(2-methoxycarbonyl)phenoxy]acetate (*Ia*) was chosen as a model compound for the investigation of this reaction. The following reagents and reaction conditions were applied in the condensations of the said compound: *a*) magnesium methoxide, ethoxide, and isopropoxide in the corresponding alcohol at the boiling temperature, *b*) sodium methoxide or potassium carbonate in boilig methanol, *c*) potassium tert-butoxide in tetrahydrofuran at room temperature, *d*) action of powdered potassium hydroxide in toluene in the presence of cetyltrimethylammonium bromide

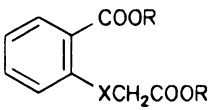
(CTMAB) under the conditions of phase-transfer catalysis at the boiling temperature. As it follows from Table I the best (and comparable) yields of methyl 3-hydroxybenzo-[*b*]furan-2-carboxylate (*IIa*) were obtained with application of potassium tert-butoxide, sodium methoxide, and magnesium methoxide. Magnesium ethoxide gave – with simultaneous transesterification – the product *IIb* in a medium yield. The application of magnesium isopropoxide only lead to transesterification giving the diisopropyl ester *Ic*. Anhydrous potassium carbonate in methanol was little effective and also ineffective was the powdered potassium hydroxide under the conditions of phase-transfer catalysis. The main reaction product was (2-carboxyphenoxy)acetic acid (*Ib*), the desired ester *IIa* being present as a minor component only.

For further investigation of the cyclization reactions of esters *Id* – *Ih* we chose only sodium methoxide, magnesium methoxide, and potassium tert-butoxide. The results are summarized in Table II. As it can be seen in the table the cyclizations of the diesters *Id* – *Ih* have comparable results. An exception was the condensation of ester *If* to indole *IIf* which reaction is negatively affected by formation of the little reactive salt resulting from the primary neutralization of the hydrogen atom in NH group with formation of the corresponding N-salt. The reaction course could not be affected in any substantial way by applying excess magnesium methoxide or more basic alkoxides. This finding agrees with the behaviour of similar compounds observed earlier[8,24]. On the other hand, the N-methyl ester *Ig* again undergoes the cyclization reaction quite smoothly to give the ester *IIg*.

TABLE I
Conditions and results of cyclization of diester *Ia*

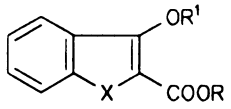
Base	Solvent	Reaction time min	Temperature °C	Product	Yield %
$(MeO)_2Mg$	methanol	90	65	*IIa*	70[a]
$(EtO)_2Mg$	ethanol	90	78	*IIb*	40[b]
$(i\text{-}PrO)_2Mg$	2-propanol	90	85	*Ic*	90
MeONa	methanol	45	65	*IIa*	77
K_2CO_3	methanol	120	65	*IIa*	29
t-BuOK	THF	120	20	*IIa*	70
KOH/CTMAB[c]	toluene	120	110	*IIa*	7
				Ib	72[d]

[a] M.p. 109 – 110 °C, ref.[7] 105 – 106 °C; [b] m.p. 62 – 64.5 °C, ref.[7] 65 °C; [c] 10 mole % of hexadecyltrimethylammonium bromide; [d] m.p. 191 – 193 °C, ref.[23] 190 – 192 °C.



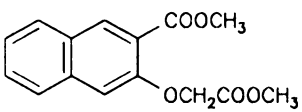
I

I	X	R
a	O	CH_3
b	O	H
c	O	$(CH_3)_2CH$
d	S	CH_3
e	SO_2	CH_3
f	NH	CH_3
g	NCH_3	CH_3



II

II	X	R	R^1
a	O	CH_3	H
b	O	C_2H_5	H
c	S	H	CH_2COOH
d	S	CH_3	H
e	SO_2	CH_3	H
f	NH	CH_3	H
g	NCH_3	CH_3	H
i	O	CH_3	CH_2COOCH_3
j	S	CH_3	CH_2COOCH_3
k	NCH_3	CH_3	CH_2COOCH_3
l	S	H	CH_3



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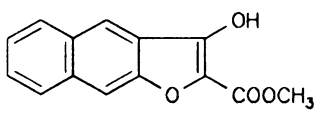
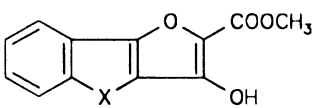


IIh



III

III	X
a	O
b	S
c	NCH_3

In accordance with ref.[7] the ester *IIa* is in equilibrium with its keto form. The presence of keto forms was not found in the enol esters *IId* – *IIh* by means of spectroscopy.

Furthermore, from Tables I and II it follows that the yields of the products *II* are connected with the nature of the heteroatom in the esters *I* and *II* and increase in the order O ≈ SO_2 < N–CH_3 ≈ S. This dependence agrees with the increasing stability of the heterocyclic compound formed and with the stabilization[25 – 28] of the intermediate carbanions of the condensation reaction by the adjacent heteroatoms. From the results obtained it can be unequivocally concluded that, in the condensation reactions of the esters type *I*, magnesium methoxide is a fully effective and advantageous reagent of comparable effectivity with alkali alkoxides.

The formation of a further – furan – heterocyclic system was accomplished after the alkylation of the esters *IIa*, *IId*, *IIg* at the 3 position by means of methyl chloroacetate. The alkylation of ester *IIa* was carried out either in the presence of potassium carbonate in acetone or by action of sodium hydride in dimethylformamide, the latter way giving a higher yield (46% or 62%, respectively) of methyl [2-(methoxycarbonyl)benzo[*b*]-

TABLE II
Conditions and results of cyclizations of diesters *Id* – *Ih*

Ester	Base	Reaction time min	Product	Yield %	M.p., °C
Id	$(MeO)_2Mg$	30[a]	*IId*	92	102.5 – 104.5[b]
	MeONa	30[a]		90	
	t-BuOK	120[c]		85	
Ie	$(MeO)_2Mg$	30[a]	*IIe*	76	180 – 183[d]
	MeONa	30[a]		65	
	t-BuOK	120[c]		60	
If	$(MeO)_2Mg$	30[a]	*IIf*	[e]	
	MeONa	30[a]		35	158 – 159[f]
	t-BuOK	120[c]		37	
Ig	$(MeO)_2Mg$	30[a]	*IIg*	95	149.5 – 151[g]
	MeONa	30[a]		94	
	t-BuOK	120[c]		80	
Ih	$(MeO)_2Mg$	30[a]	*IIh*	62	159.5 – 160.5[h]
	MeONa	30[a]		65	

[a] In boiling methanol; [b] ref.[7] 107 – 108 °C; [c] in THF at 20 °C; [d] ref.[35] 190 – 191 °C; [e] identified by TLC; [f] ref.[7] 157 – 158 °C; [g] ref.[3] 144 – 146 °C; [h] ref.[32] 162 °C.

furan-3-yloxy]acetate (*IIi*). With sodium hydride, the yields of esters *IIj* and *IIk* were good.

The attempts at the Dieckmann condensation of ester *IIi* were not successful in our case. The desired product *IIIa* was not found after application of sodium methoxide, magnesium methoxide, and potassium tert-butoxide under various reaction conditions. The reproduction of this reaction under the conditions given in ref.[29] also gave an unsatisfactory result. In all the cases, only polymeric material was isolated. On the other hand, the cyclization reaction of esters *IIj* and *IIk* by action of potassium tert-butoxide in a benzene–tetrahydrofuran mixture was successful and gave the respective hydroxyesters *IIIb* and *IIIc*. The other above-mentioned bases were ineffective. The attempt at the cyclization of ester *IIj* by action of powdered potassium hydroxide in toluene under the conditions of phase-transfer catalysis only resulted in hydrolysis to give (2-carboxybenzo[*b*]thiophen-3-yloxy)acetic acid (*IIc*). It was found that this acid, when heated above its melting point, is selectively decarboxylated to 3-methoxybenzo[*b*]thiophene-2-carboxylic acid (*III*). The structure of *III* was confirmed by spectral methods and also by the synthesis involving the methylation of hydroxyl group of ester *IId* and subsequent saponification of the ester function.

Sodium hydride was also unsuccessful in the cyclization of ester *IIj*. We isolated a small amount (4%) of the dealkylation product – ester *IId* – beside the starting material *IIj*. An analogous dealkylation reaction was also observed during the attempt at cyclization of ester *Ia* by action of sodium hydride: the mother liquor after isolation of ester *IIa* contained small amounts of methyl salicylate. The mentioned behaviour of sodium hydride is quite unique, no analogous case of splitting of ether linkage by sodium hydride was found in literature except in one report[31].

When interpreting the ^{1}H NMR spectra of esters *IIIb* and *IIIc* we proved that compound *IIIb* is fully enolized in solution, ester *IIIc* being a 9 : 1 mixture of enol and keto forms.

The structure of all the compounds *II* and *III* synthesized was verified by NMR, IR and mass spectra and by elemental analysis.

EXPERIMENTAL

The temperature data were not corrected. The gas chromatography was carried out on a Chrom 5 apparatus (Laboratorní přístroje Praha; FID, carrier of stationary phase Gaschrom Q, carrier gas nitrogen). The IR spectra were measured with a Perkin–Elmer 325 apparatus in chloroform, the absorption wavenumber values are given in cm^{-1}. The ^{1}H NMR spectra were measured with a Bruker 400 apparatus in deuteriochloroform with TMS as the internal standard; the chemical shifts are given in ppm. The mass spectra were measured with a JEOL DX 300 apparatus (electron energy 70 eV).

Chemicals: Methyl [(2-methoxycarbonyl)phenoxy]acetate (*Ia*, b.p. 135 – 139 °C/27 Pa, m.p. 48 – 50 °C), methyl [(2-methoxycarbonyl)phenylthio]acetate (*Ie*, m.p. 99 – 101 °C), methyl [N-(2-methoxycarbonyl)-phenyl]glycinate (*If*, m.p. 94 – 96 °C), methyl [N-(2-methoxycarbonylphenyl)-N-methyl]glycinate (*Ig*, b.p. 132 – 135 °C/40 Pa), and methyl [(3-methoxycarbonyl)-2-naphthyloxy]acetate (*Ih*, m.p. 70 – 71 °C) were prepared by standard procedures[3,7,32 – 36]. The solutions of magnesium methoxide, ethoxide, and

isopropoxide were prepared by the reaction of the required amount of magnesium in the respective alcohol in the presence of a catalytic amount of iodine or $HgCl_2$ (for magnesium isopropoxide).

Dieckmann Condensation of Esters *Ia*, *Id – Ih*

A mixture of the corresponding base (15 mmol) and solvent (Tables I and II) was stirred under nitrogen and treated with 10 mmol ester. The mixture was stirred at room temperature (potassium tert-butoxide) or refluxed, cooled, poured into 200 ml ice water, and acidified with 5% hydrochloric acid to pH 2. The solid was collected by filtration, washed with water, and recrystallized from methanol to isolate the esters *IIa*, *IIb*, *IId – IIh*.

Methyl [(2-Methoxycarbonyl)benzo[*b*]furan-3-yloxy]acetate (*IIi*)

Procedure A: An amount of 4.0 g (35 mmol) methyl chloroacetate was added dropwise to a mixture of 3.1 g (16 mmol) ester *IIa*, 2.75 g (20 mmol) anhydrous potassium carbonate, and 40 ml acetone with stirring during 10 min. The suspension was boiled 39 h, cooled, filtered, the solid was washed with 40 ml acetone, and the solution was evaporated. The crystallization of the residue from methanol gave 1.95 g (46%) compound *IIi*, m.p. 75.6 – 76.5 °C. For $C_{13}H_{12}O_6$ (264.2) calculated: 59.10% C, 4.32% H; found: 59.13% C, 4.40% H. IR spectrum: ν(C=O) 1 755 and 1 710 cm^{-1}. ^1H NMR spectrum: 3.79 s, 3 H (OCH_3); 3.97 s, 3 H (OCH_3); 5.09 s, 2 H (CH_2); 7.29 – 7.80 m, 4 H (arom.).

Procedure B: A solution of 4.0 g (21 mmol) ester *IIa* in 20 ml dimethylformamide was added drop by drop to a suspension of 0.72 g (33 mmol) sodium hydride in 30 ml dimethylformamide under nitrogen with stirring and cooling in an ice bath. After 30 min stirring, 5.0 g (46 mmol) methyl chloroacetate was added dropwise and the mixture was heated on a water bath for 1 h. After cooling, the mixture was diluted with 200 ml water and washed with 3 × 50 ml ether. The ethereal solution was washed with water, salt solution, and dried with magnesium sulfate. The solvent was evaporated, and the residue was recrystallized from methanol to give 3.43 g (62%) ester *IIi*.

Methyl [(2-Methoxycarbonyl)benzo[*b*]thiophen-3-yloxy]acetate (*IIj*)

The same procedure *B* as that above-applied to preparation of diester *IIi* was used to obtain, from 2.1g (10 mmol) ester *IId*, 1.57 g (56%) ester *IIj*, after recrystallization from methanol m.p. 95 – 96 °C (ref.[30] gives m.p. 98 – 99 °C). Mass spectrum (*m/z*, % rel. int.): 282 (4) [M^+], 280 (72), 249 (7), 223 (3), 221 (44), 207 (24), 191 (8), 189 (100), 179 (30), 161 (8), 151 (50), 136 (20), 120 (34), 104 (12), 77 (6).

Methyl [(2-Methoxycarbonyl)-N-methylindol-3-yloxy]acetate (*IIk*)

An analogous procedure *B* to that used for diester *IIi* was applied to 3.5 g (17 mmol) ester *IIg* to give 2.5 g (53%) ester *IIk*, m.p. 64 – 65 °C (methanol). For $C_{14}H_{15}NO_5$ (277.3) calculated: 60.64% C, 5.45% H, 5.05% N; found: 60.37% C, 5.41% H, 4.99% N. IR spectrum ν(C=O) 1 735 and 1 700 cm^{-1}. ^1H NMR spectrum: 3.84 s, 3 H (NCH_3); 3.97 s, 3 H (OCH_3); 3.99 s, 3 H (OCH_3); 4.78 s, 2 H (CH_2); 7.10 – 7.80 m, 4 H (arom.).

Methyl 3-Hydroxybenzothieno[3,2-*b*]furan-2-carboxylate (*IIIb*)

A solution of 2.0 g (7 mmol) ester *IIj* in 50 ml benzene was stirred at 0 °C under nitrogen, and 12 ml 1.42 M potassium tert-butoxide solution in THF was added thereto drop by drop during 10 min. The mixture was heated on water bath 4 h, decomposed with 200 ml ice water, and washed with 50 ml chloroform. After acidification with aqueous 5% hydrochloric acid, the solid was collected by filtration, washed with water, and recrystallized from methanol to give 1.10 g (63%) compound *IIIb*, m.p. 122 – 123 °C (ref.[30] gives m.p.

124 – 125 °C). Mass spectrum (*m/z*, % rel. int.): 210 (2), 208 (38), 178 (6), 176 (100), 148 (4), 120 (48), 104 (14), 77 (12).

Methyl 3-Hydroxy-4-methyl-4*H*-furo[3,2-*b*]indole-2-carboxylate (*IIIc*)

Analogous procedure to that used for ester *IIIb* was applied to 1.0 g (3.6 mmol) ester *IIk* to give 0.51 g (58%) ester *IIIc*, m.p. 137 – 138 °C (methanol). For $C_{13}H_{11}NO_4$ (245.2) calculated: 63.68% C, 4.52% H, 5.71% N; found: 63.75% C, 4.84% H, 5.69% N. IR spectrum: ν(C=O) 1 750 and 1 700 cm^{-1}. ^1H NMR spectrum: 3.79 s, 2.7 H (OCH_3); 3.88 s (NCH_3); 3.99 s, 0.3 H (OCH_3); 5.52 s, 0.9 H (OH); 7.13 – 7.77 m, 4 H (arom.).

[2-Carboxybenzo[*b*]thiophen-3-yloxy]acetic Acid (*IIc*)

A mixture of 0.53 g (2 mmol) ester *IIi*, 0.22 g (4 mmol) powdered potassium hydroxide, 0.07 g (0.2 mmol) cetyltrimethylammonium bromide, and 15 ml toluene was refluxed with stirring 4 h, cooled, diluted with 100 ml water, and the aqueous solution was acidified with 5% hydrochloric acid to pH 2. The separated solid was collected by filtration, washed with water, and recrystallized from methanol to give 0.30 g (60%) diacid *IIc*, m.p. 224 – 225 °C (decomp.). For $C_{11}H_8O_5S$ (252.2) calculated: 52.39% C, 3.20% H, 12.69% S; found: 53.07% C, 3.42% H, 12.31% S. IR spectrum: ν(C=O) 1 740 and 1 705 cm^{-1}. ^1H NMR spectrum: 5.02 s (CH_2); 7.49 – 8.00 m, 4 H (arom.); 13.23 bs, 1 H (COOH). Mass spectrum (*m/z*, % rel. int.): 254 (6) [M + 2], 252 (99) [M^+], 208 (13), 193 (26), 189 (36), 176 (100), 149 (46), 137 (30), 121 (90).

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