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Efficient Synthesis of 1-Alkoxycarbonyl-Methyl-2-Alkylpyrroles from Dichloro- and Methoxychloropropylalkyl Ketones

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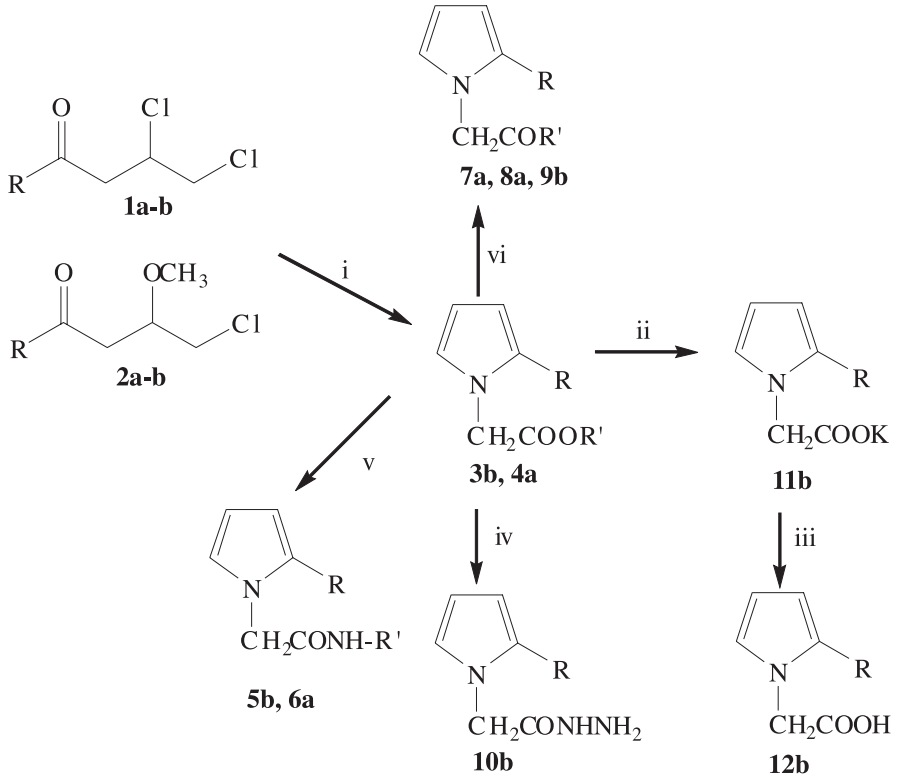
The condensation reaction of 2,3-dichloropropyl- and 2-methoxy-3-chloropropyl alkyl ketones with alkyl 2-aminoacetate salts leads to 1-alkoxy-carbonylmethyl-2-alkylpyrroles. These compounds, with various bases, gave 1-carbamoylmethyl-, 1-dialkylaminocarbonylmethyl-, 1-carbazoyl methyl-2-alkylpyrroles and potassium salt of 2-alkyl-pyrrolyl-1-acetic acid.

Introduction

Pyrrole derivatives of amines and amino acids are important starting materials for the synthesis of many different biologically active compounds. A stereoselective synthesis of indolizidine alkaloids, based on the reduction of bicyclic pyrroles, has been reported[1]. Paal-Knorr synthesis starting from primary amines and 1,4-dicarbonyl compounds and their masked equivalents, such as tetrahydro-2,5-dimethoxyfuran, is often used for the construction of pyrrole rings[2]. It was previously reported that an interaction of 2,3-dichloropropylalkyl ketones with primary amines and their functionally substituted derivatives leads to N-substituted derivatives of pyrroles[3−5], while a reaction of 3-chloropropenylalkyl ketones with hydrazine hydrate leads to 1-amino-2-alkylpyrroles[6] and that of alkyl(trans-2-methoxycyclopropyl) ketones, products of 1,3-dehydrochlorination of 2-methoxy-3-chloropropylalkyl ketones, with primary amines, leads to N-substituted 2-alkylpyrroles[7]. It was also established that different substituted pyrrole rings can be constructed from amines, amino alcohols and amino acids with various chloroenones in basic medium[8].

In this paper, we describe the condensation reaction of 2,3-dichloropropylalkyl ketones **1a-b** and 2-methoxy-3-chloropropylalkyl ketones **2a-b** with alkyl 2-aminoacetate salts, which allows the synthesis of 1-alkoxycarbonylmethyl-2-alkylpyrroles **3b** and **4a** (80-81%) (Figure 1) in water-benzene medium at 20-25°C followed by reflux for 6 hours[9].



i= NH_2CH_2COOR', Na_2CO_3, benzene, H_2O, Et_3N, ii= KOH, MeOH or EtOH,
iii= 10% HCl, iv= NH_2NH_2, EtOH, v= NH_2-R', EtOH, vi= H-R'
a R= CH_3, b R= C_2H_5
R'= CH_3 (3b), C_2H_5 (4a), H (5b), $CH_2C_6H_5$ (6a), $N(C_2H_5)_2$ (7a), piperidino (8a), morpholino (9b)

Figure 1

Results and Discussion

An interaction of 1-alkoxycarbonylmethyl-2-alkylpyrroles with ammonia, primary and secondary amines in alcohol or dioxane leads to the formation of respective amido-derivatives of pyrrole. It was found that the relative reactivity of 1-alkoxy carbonylmethyl-2-alkylpyrroles with ammonia or primary amines is faster than with secondary amines. Thus, for example, the reaction of **3b** and **4a** with ammonia proceeds easily to give 2-(2-ethyl-1*H*-pyrrol-1-yl)acetamide **5b** (80%) at 35-45°C in 4 hours and *N*-benzyl-2-(2-methyl-1*H*-pyrrol-1-yl)acetamide **6a** (74%) at 50-55°C in 5 hours, respectively. Similar treatment of **3b** and **4a** with secondary amines gave *N*,*N*-diethyl-2-(2-methyl-1*H*-pyrrol-1-yl)acetamide **7a** (73%), 2-(2-methyl-1*H*-pyrrol-1-yl)-1-piperidin-1-ylethan-1-one **8a** (82%) and 2-(2-methyl-1*H*-pyrrol-1-yl)-1-morpholin-4-ylethan-1-one **9b** (79%) at 75-80°C in 8 hours. 2-(2-Ethyl-1*H*-pyrrol-1-yl)acetohydrazide **10b** was synthesized by heating **3b** with excess hydrazine hydrate in ethanol for 6 hours (75%). When **3b** was heated with ethanol solution of potassium hydroxide at 55-60°C for 6 hours, the potassium salt of 2-(2-ethyl-1*H*-pyrrol-1-yl)acetic acid **11b** was formed (85%), which was then converted to the related acid, 2-(2-ethyl-1*H*-pyrrol-1-yl)acetic acid, **12b** with 10% HCl solution.

In summary, a simple and efficient synthesis of 1-alkoxycarbonyl-methyl-2-alkylpyrroles is achieved by treating alkyl 2-aminoacetate salts with dichloro- and methoxychloropropylalkyl ketones where a C-N bond

formation takes place by removal of chloride ion, followed by a cyclization and elimination reaction to give the pyrroles[13].

Experimental

IR spectra were obtained on the apparatus UR-20 or Specord M 80 in thin layer or vaseline oil. NMR spectra were recorded on the apparatus Tesla BS-487B (80MHz) in $(CD_3)_2CO$, internal standard TMS.

2,3-dichloropropylalkyl ketones, **1a-b**, were prepared by electrophilic addition of chloroanhydrides of carboxylic acids to allyl chloride in the presence of aluminum chloride in dichloromethane at -15 °C and 2-methoxy-3-chloropropylalkyl ketones, **2a-b**, by the addition of methanol to 3-chloropropenyl alkylketones[9,12].

1-Alkoxycarbonylmethyl-2-pyrroles

A: To a solution of 0.1 mol alkyl 2-aminoacetate salt in 50 ml of water was added dropwise 6 g of (0.55 mol) sodium carbonate dissolved in 50 ml of water, 0.1 mol of 2,3-dichloropropylalkyl ketone in 100 ml of benzene and 28 ml of (0.2 mol) triethylamine at 20-25°C. The reaction mixture was refluxed for 6 hours. After cooling, the organic layer was separated, washed with water, dried over $MgSO_4$ and distilled under vacuum (Tables 1, 2).

B: To a solution of 0.1 mol alkyl 2-aminoacetate salt in 50 ml of water, was added dropwise 6 g of (0.55 mol) sodium carbonate dissolved in 50 ml of water, 0.1 mol of 2-methoxy-3-chloropropylalkyl ketone dissolved in 100 ml of benzene and 14 ml (0.1 mol) of triethylamine at 20-25°C. Then the mixture was refluxed for 6 hours. The separation and purification were carried out as described previously. According to the data, the samples of **3b**, **4a** are identical to the pyrroles prepared by method A (Tables 1, 2).

2-(2-Ethyl-1*H*-pyrrol-1-yl)acetamide 5b

Through a solution of 0.05 mol of methyl 2-(2-ethyl-1*H*-pyrrol-1-yl)acetate **3b** in 100 ml of methyl or ethyl alcohol was passed ammonia until saturation at 35-40°C for 4 hours. After cooling of the reaction mixture to room temperature, 100 ml of ethyl acetate was added, and the precipitate formed was filtered and recrystallized from heptane.

***N*-Benzyl-2-(2-methyl-1*H*-pyrrol-1-yl)acetamide 6a**

A solution of 0.05 mol of benzylamine and 0.05 mol of ethyl 2-(2-methyl-1*H*-pyrrol-1-yl)acetate **4a** in 50 ml alcohol or dioxane was heated at 50-55°C for 5 hours. After cooling the mixture, crystals were precipitated with ethyl acetate, filtered and recrystallized from heptane.

***N*,*N*-diethyl-2-(2-methyl-1*H*-pyrrol-1-yl)acetamide 7a, 2-(2-methyl-1*H*-pyrrol-1-yl)-1-piperidin-1-ylethan-1-one 8a and 2-(2-methyl-1*H*-pyrrol-1-yl)-1-morpholin-4-ylethan-1-one 9b**

A solution of 0.05 mol of N,N-diethylamine, piperidine or morpholine and 0.05 mol of **3b** or **4a** in 50 ml of ethanol or dioxane was heated at 75-80°C for 8 hours. After cooling the mixture, crystals were precipitated with ethyl acetate, filtered and recrystallized from heptane.

2-(2-Ethyl-1*H*-pyrrol-1-yl)acetohydrazide 10b

To a solution of 6 ml of (0.06 mol) hydrazin hydrate in 25 ml of methyl or ethyl alcohol was added dropwise 0.05 mol of methyl 2-(2-ethyl-1*H*-pyrrol-1-yl)acetate **3b** dissolved in 25 ml of ethanol. The reaction mixture was refluxed for 6 hours, cooled, and crystals were precipitated with ethyl acetate, filtered and recrystallized from heptane.

Potassium salt of 2-(2-ethyl-1*H*-pyrrol-1-yl)acetic acid 11b

To a solution of 0.05 mol of potassium hydroxide in 100 ml of methyl or ethyl alcohol at 55-60°C was added dropwise 0.05 mol of methyl 2-(2-ethyl-1*H*-pyrrol-1-yl)acetate **3b** dissolved in 25 ml of alcohol. The reaction mixture was mixed at same temperature for 6 hours. On cooling, 2/3 of the alcohol was evaporated, to the residue 100 ml of ethyl acetate was added, and the separated crystals were filtered, washed with ether and dried.

2-(2-Ethyl-1*H*-pyrrol-1-yl)acetic acid 12b

To a solution of 0.05 mol of potassium salt of 2-(2-ethyl-1*H*-pyrrol-1-yl)acetic acid in 25 ml of water was added dropwise 20 ml of 10% HCl at 20-26°C. The reaction mixture was extracted with methylene chloride, the the extract was washed with water and dried over $MgSO_4$. After evaporation of the solvent, crystals were recrystallized from methyl alcohol.

Table 1. ^{1}H NMR spectra of synthesized compounds

compound	3-H	4-H	5-H	N-CH_2	R	R′
3b	5.67	5.82	6.30	4.30	1.10 t, 3.40 q	3.54 s
4a	5.65	5.80	6.25	4.12	1.90 s	1.01 t, 4.15 q
5b	5.60	5.76	6.43	4.30	1.52 t, 2.35 q	4.73 s
6a	5.62	5.83	6.42	4.38	1.94 s	4.20, 7.20 s
7a	5.50	5.63	6.75	4.09	1.84 s	0.85 t, 2.45 q
8a	5.58	5.70	6.33	4.75	1.90 s	1.40 m, 3.30 m
9b	5.57	5.75	6.35	4.70	1.34 t, 2.63 q	2.22 t, 3.50 q
10b	5.63	5.75	6.42	4.75	1.31 t, 2.91 q	2.81 br s, 9.40 br s
11b	5.80	6.34	6.90	4.70	1.27 t, 2.74 q	-
12b	5.61	6.30	6.82	4.64	1.40 t, 2.83 q	10.6 s

Table 2. Experimental data for synthesized compounds

Compound	Formula	bp°C (mp°C)	Yield (%)	Elemental analysis Calcd. C H N (%)	& Found C H N (%)
3b	$C_9H_{13}NO_2$	94-95 (3mmHg)	81	64.67 7.78 8.36	64.13 8.01 8.53
4a	$C_9H_{13}NO_2$	92-93 (2mmHg)	80	64.67 7.78 8.36	65.09 7.68 8.19
5b	$C_8H_{12}N_2O$	(125-126)	80	63.16 7.89 18.42	62.90 8.07 18.10
6a	$C_{14}H_{16}N_2O$	(100-102)	74	73.68 7.02 12.28	73.11 7.12 12.61
7a	$C_{12}H_{28}N_2O$	(70-71)	73	69.23 9.61 13.46	70.04 9.87 13.89
8a	$C_{12}H_{18}N_2O$	(105-106)	82	69.90 8.73 13.59	70.39 8.91 12.76
9b	$C_{12}H_{18}N_2O_2$	(104-106)	79	64.86 8.11 12.61	65.17 8.39 12.29
10b	$C_8H_{13}N_3O$	(118-119)	75	57.48 7.78 25.15	57.92 8.04 24.86
11b	$C_8H_{10}NO_2K$	(261-263)	85	50.26 5.23 7.33	50.79 5.41 7.60
12b	$C_8H_{11}NO_2$	(144-146)	52	62.74 7.19 9.21	62.97 7.36 9.47

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