A Convenient and Efficient Conversion of Diethyl [[[2-(3- or 4-Pyridinyl)-4-pyrimidinyl]amino]methylene]propanedioates to Higher Homologs by Base-Catalysed Transesterification

Baldev Singh

Sterling-Winthrop Research Institute,
Rensselaer, New York 12144, USA

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Base-catalysed transesterification of diethyl [[[2-(3- or 4-pyridinyl)-4-pyrimidinyl]amino]methylene]propanedioates gave higher homolog esters in high yields.

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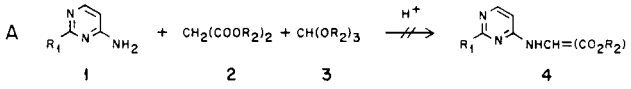
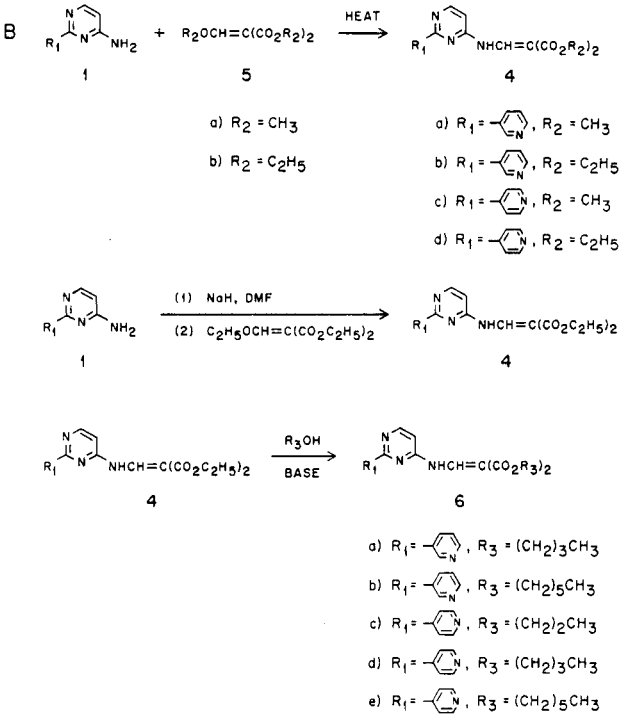
We have recently reported [1] the synthesis of dimethyl and diethyl [[[2-(3- or 4-pyridinyl)-4-pyrimidinyl]amino]-methylene]propanedioates **4** which are orally active inhibitors of passive cutaneous anaphylaxis in rats. The higher homologs of these esters **4** were needed for structure-activity relationship studies. Compounds of type **4** can be prepared by two methods: (A) by the acid-catalysed condensation between an amine, dialkyl propanedioate and trialkyl orthoformate or (B) by the reaction between an amine and dialkyl (alkoxymethylene)propanedioate. The amines **1** failed to undergo the former reaction in a satisfactory manner due to lack of reactivity of the amino group but they did react with dimethyl (methoxymethylene)propanedioate (**5a**) and diethyl (ethoxymethylene)propanedioate (**5b**) [1] at 140-170° to afford the respective compounds **4** in 60-80% yield. However, high temperatures caused the decomposition of the products which made the isolation of the pure products a tedious process involving chromatography or repeated crystallizations.



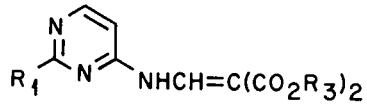
1 2 3 4



1 5 4

4 6

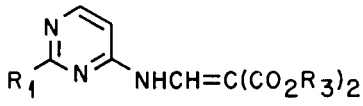
Table 1



No.	R_1	R_3	Crystallization Solvent	Yield [%] [a]	Mp [b]	Molecular Formula	Analysis Calcd. (Found) C	H	N
6a	3-pyridinyl	$(CH_2)_3CH_3$	hexane	74	85-87	$C_{21}H_{26}N_4O_4$	63.30	6.58	14.06
							(62.97	6.51	14.15)
6b	3-pyridinyl	$(CH_2)_5CH_3$	hexane	80	83-85	$C_{25}H_{34}N_4O_4$	—	—	—
							—	—	—
6c	4-pyridinyl	$(CH_2)_2CH_3$	hexane-ether	78	117-119	$C_{19}H_{22}N_4O_4$	61.61	5.99	15.13
							(63.36	6.75	14.01)
6d	4-pyridinyl	$(CH_2)_3CH_3$	hexane-ether	70	93-95	$C_{21}H_{26}N_4O_4$	63.30	6.58	14.06
							(63.36	6.75	14.01)
6e	4-pyridinyl	$(CH_2)_5CH_3$	hexane	77	85-87	$C_{25}H_{34}N_4O_4$	66.06	7.54	12.33
							(66.38	7.53	12.43)

[a] Yields reported are those of pure isolated products. [b] Melting points are uncorrected and were determined in open capallaries in an oil bath.

Table 2



No.	NH d [b], 1H	CH d, 1H	JNC [Hz]	H-5 d, 1H	H-6 d, 1H	$J_{5,6}$ [Hz]	OCH_2- t, 4H
6a	11.06	9.21	12	6.76	8.64	6	4.30
6b	11.07	9.20	13	6.76	8.64	6	4.30
6c	11.1	9.30	13	6.82	8.67	6	4.29, 4.27
6d	11.09	9.25	12	6.82	8.65	6	4.32
6e	11.08	9.23	12	6.80	8.64	6	4.29

[a] The nmr spectra were recorded on Varian HA-100 spectrometer in deuteriochloroform using tetramethylsilane as the internal standard, chemical shifts are reported in ppm and are given in δ units. [b] Broad.

An alternative route [2] employing the reaction between the sodium salts of the amines **1** and diethyl (ethoxymethylene)propanedioate (**5b**) in dimethylformamide at low temperatures afforded pure products in yields greater than 80%. Unfortunately, only dimethyl (methoxymethylene)propanedioate (**5a**) and diethyl (ethoxymethylene)-propanedioate (**5b**) are available commercially. The higher homologs have to be synthesized. Since we had large quantities of **4b** and **4d** at hand [2], we thought it advantageous to convert them to their higher homologs by transesterification. There was no acid-catalysed transesterification at lower temperatures ($<30°$) whereas higher temperatures ($>50°$) resulted in decomposition products, which is not surprising due to the labile nature of -NH-CH=C= group. However, base-catalysed transesterification at room temperature over a prolonged period afforded good yields of higher esters **6**. This procedure would be useful in the synthesis of related compounds which are not readily accessible by other methods.

EXPERIMENTAL

The General Procedure is Illustrated by the Preparation of Dihexyl [[[2-(3-Pyridinyl)-4-pyrimidinyl]amino]methylene]propanedioate (**6b**).

A stirred solution of 17.1 g (0.05 mole) of **4b** and 400 ml of 1-hexanol was treated with 0.5 g of 50% sodium hydride/oil and then left at room temperature for 120 hours. The resulting pale yellow solution was treated with 2 ml of glacial acetic acid and concentrated on a rotary evaporator to give a pale yellow semisolid residue which was dissolved in 300 ml of ether and filtered through a supercel pad to remove sodium acetate. The filtrate was concentrated to dryness on a rotary evaporator and the product was crystallized from hexane to afford 18.2 g (80%) of **6b** as pale yellow flakes, mp 83-85°.

Anal. Calcd. for $C_{25}H_{34}N_4O_4$: C, 66.06; H, 7.54; N, 12.33. Found: C, 66.08; H, 7.55; N, 12.27.

Acknowledgements.

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REFERENCES AND NOTES

[1] G. Y. Lesher, B. Singh, Z. E. Mielens, *J. Med. Chem.*, **25**, 837 (1982).

[2] B. Singh, G. Y. Lesher, *J. Heterocyclic Chem.*, **19**, 1581 (1982).