Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 23 Sep 2006.

To cite this article: M. N. Deshmukh, U. Sampath Kumar & A. V. Rama Rao (1995): Titanium Mediated Cyclization of N-Substituted Di(β-Carbethoxyethyl)amines: Preparation of 1-Substituted-3-carbethoxy-4-piperidones, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 25:2, 177-182

To link to this article: http://dx.doi.org/10.1080/00397919508010804

SYNTHETIC COMMUNICATIONS, 25(2), 177-182 (1995)

TITANIUM MEDIATED CYCLIZATION OF N-SUBSTITUTED DI(β-CARBETHOXYETHYL)AMINES : PREPARATION OF 1-SUBSTITUTED-3-CARBETHOXY-4-PIPERIDONES

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Abstract : Dieckmann cyclisation of N-substituted di(β-carbethoxyethyl)amines with titanium tetrachloride in DCM in the presence of triethylamine leads to the formation of 3-carbethoxy-4-piperidones.

The preparation of N-substituted piperidones (**2**) from the N-substituted di(β-carbethoxyethyl) amines by Dieckmann condensation[1-6] is a well documented synthetic strategy. This approach requires drastic condition involving the use of hazardous reagents such as sodium metal[1-3,6] and sodium hydride[4,5]. Although sodium alkoxide[4-6] and other bases are also known to effect Dieckmanm condensation, yield of the resultant piperidone often is much lower. Consequently, the

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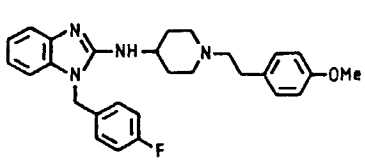
IICT Communication No. 3361.

utility of NaH is the acceptable base[4,5] to produce piperidone (**1**) on commercial scale. However, the use of sodium hydride on a large scale is somewhat hampered. Therefore, more easily performed mild methods for the synthesis of 1-substituted-3-carbethoxy-4-piperidones would be desirable.

In our attempt to develop new process technologies for the well known drugs such as astemizole (**3**, antihistamine), Loperamide (**4**, antidiarrheal) and halopyridol (**5**, antipsychotic drug), we required large quantities of the N-substituted piperidones (**2**) as the key intermediates. Therefore, we decided to look into the $TiCl_4$-promoted cyclization of **6**.



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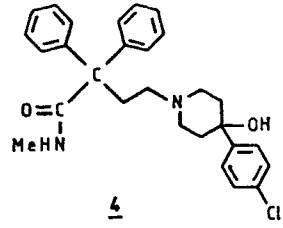

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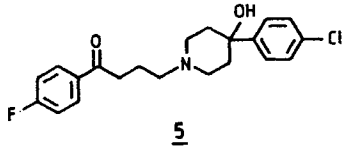

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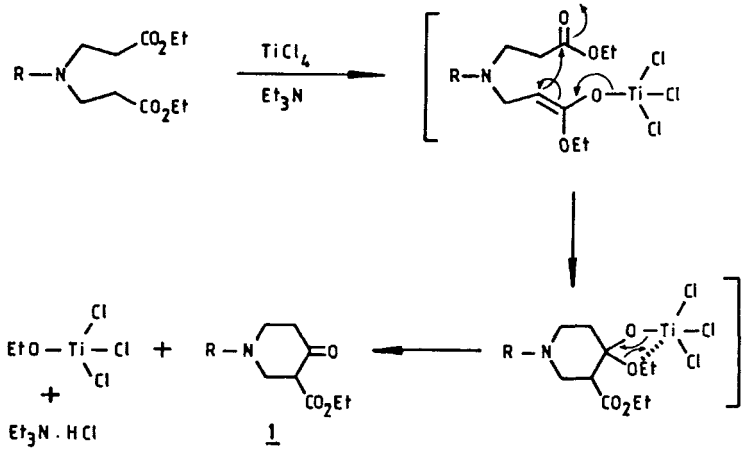
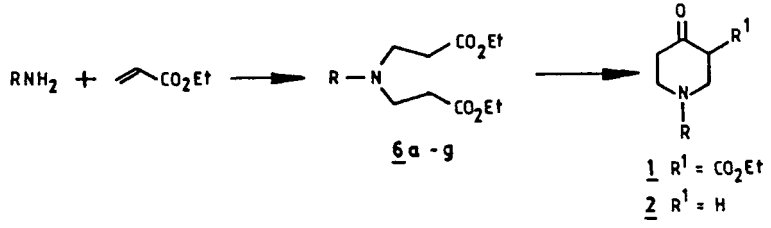
We assumed that $TiCl_4$ will react with one of the carbethoxy ethyl group to effect the enolization to give the Ti enolate. Facile elimination of alcohol from the other carbethoxy group will then afford the corresponding piperidone-3-carboxy ester (Scheme). This

Scheme :



transformation needs the presence of triethylamine as base probably to promote smooth enolization as the reaction did not proceed in the absence of Et_3N. Herein we report the preparation of different N-substituted 3-carbethoxy-4-piperidones (1) starting from N-substituted di(β -carbethoxyethyl)amines. The corresponding N-substituted-4-piperidones (2) are made by simple acid hydrolysis followed by decarboxylation as per established methods[1].



In conclusion, the mild reaction conditions of the present $TiCl_4$ mediated Dieckmann condensation is advantageous over the classical

Table

Entry[A]	R	Time (h)	% Yield[B] of **1**
6a	Me	4	79
6b	Et	4	70
6c	i-Bu	4	85
6d	$C_6H_5CH_2$	5	58
6e	$C_6H_5CH_2CH_2$	5	80
6g	p-$MeOC_6H_4CH_2CH_2$	2	85
6b	C_6H_5	4	82
6f	p-$FC_6H_4CH_2$	3	78

A. The cyclisation was carried out at -15° to -5°.

B. Yields given are for isolated products. All compounds were fully characterised by NMR, IR, MS and elemental analysis.

condensation. The condensation is of quite general application and is not materially affected by the nature of the R group. The internal condensation of the diester took place very smoothly giving in most cases fairly good yields of the piperidones (**1**). Further investigation concerning the scope of the present reaction is in progress.

Experimental

The N-substituted di(β -carbethoxymethyl)amines (**6a-6g**) were prepared[3] by refluxing the corresponding amine with excess ethyl ancrylate in ethanol. The diesters (**6a-6g**) were treated with $TiCl_4$ in presence of Et_3N according to the procedure described below to get the piperidones (**1**).

General procedure for the Dieckmann cyclisation of the diesters (6a-6g) to the piperidones (1a-1g)

In a typical reaction conducted under dry nitrogen atmosphere, the diester (**6g**) [10 mmol] in DCM (20 ml) was added to a stirred cooled 1M titanium (IV) chloride solution (10 mmol) at -15° to -5°. After 1 h at the same temperature, the reaction mixture was treated with triethylamine (3.1 ml, 22 mmol) over a period of 0.5 hr. After an additional period of 2 h at the same temperature with stirring, the reaction mixture was poured into 10% sodium chloride solution and pH of the aqueous solution adjusted to 8 by addition of triethylamine. Then, it was filtered and gelly precipitate washed with DCM (2x25 ml). The organic layer was separated from the filtrate and concentrated to get pure 1-substitute-3-carbethoxy-4-piperidones (**1g**)[7]. The results and experimental conditions are shown in the table.

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(Received in the UK 23 May 1994)