An Efficient Procedure for the Hantzsch Dihydropyridine Synthesis

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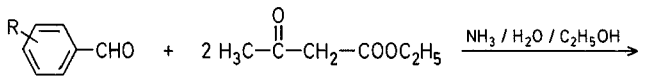
Much attention has been devoted to exploring the pharmacological utility of dihydropyridine derivatives. A variety of 1,4-dihydropyridine-3,5-dicarboxylic esters (**3**) and analogues have been prepared along this line[1]. The three-component reaction known as Hantzsch method which involves the reaction of a β-ketoester with an aldehyde and ammonia are widely utilized for the synthesis of these dihydropyridine derivatives. However, the yields of 1,4-dihydropyridines obtained by the Hantzsch method are generally low when sterically hindered aldehydes such as *o*-substituted benzaldehydes are employed. We report here a simple and efficient modification of the Hantzsch reaction using an autoclave.



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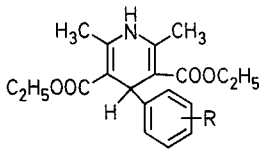

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acetoacetate and aqueous ammonia at 110 °C in an autoclave to give the expected Hantzsch esters **3** in good yields. In general, the present reaction using an autoclave gave much better results than the usual Hantzsch procedure. The Hantzsch reaction has already earlier been carried out in sealed tubes[2], the yields being generally moderate, however. In the case of 2-methylbenzaldehyde, only a 9% yield of the dihydropyridine **3d** was obtained whereas our procedure afforded the same product in 70% yield.

In conclusion, the present modification is a convenient alternative for the synthesis of Hantzsch-type 1,4-dihydropyridine derivatives bearing bulky substituents at the 4-position.

Diethyl 2,6-Dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates (3); General Procedure:

An autoclave of 100 ml capacity is successively charged with a substituted benzaldehyde (10 mmol), ethyl acetoacetate (22 mmol), ethanol (10 ml), and 28% aqueous ammonia (12 mmol). The autoclave is closed and heated at 110 °C. After cooling, the contents are transferred to a flask and volatile materials are removed using a rotary evaporator. The residual product is either recrystallized from aqueous ethanol or column-chromatographed on silica gel (ethyl acetate/hexane) and then recrystallized to give the pure product **3**.

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Table. Diethyl 2,6-Dimethyl-4-aryl-1,4-dihydropyridine-3,5-dicarboxylates (**3**) prepared

3	R	Reaction conditions [°C], [h]	Yield[a] Present method	Yield[a] Usual method[b]	m.p. [°C]	Molecular formula[c] or m.p. [°C] reported
a	2-C_6H_5—CH_2—O—	120°, 18	78	41	133–135°	$C_{26}H_{29}NO_5$ (435.5)
b	2-Cl	110°, 17	92	62[2], 39[3]	122.5–123°	123–125°[3]
c	2-OC_2H_5	110°, 19	89		121.5–122°	$C_{21}H_{27}NO_5$ (373.45)
d	2-CH_3	110°, 25	70	9[2], 67	113–114°	114°[2]
e	2,4-di-Cl	110°, 17	87		142–143°	$C_{19}H_{21}Cl_2NO_4$[d] (398.3)
f	2,3-di-OCH_3	110°, 25	79	64[4], 39	129–129.5°	133°[4]
g	2,6-di-Cl	110°, 20	37	11[3]	133–134°	133–135°[3]
		110°, 45	52			

[a] All products gave the expected I.R. and ^{1}H-N.M.R. spectra.
[b] Yields given without reference are those obtained in our comparative experiments.
[c] The microanalyses of the new compounds and of compound **3e** were in satisfactory agreement with the calculated values: C, ±0.33; H, ±0.31; N, ±0.29.
[d] This compound was reported in Ref.[5] without notation of m.p.

Examinations of solvent and temperature effects on the original Hantzsch reaction encouraged us to use a sealed system in order to increase the reaction temperature of a mixture of the components in ethanol. Thus, 2,3-dimethoxybenzaldehyde (**1f**) in ethanol was treated with ethyl acetoacetate (**2**) and 28% aqueous ammonia in an autoclave at 110 °C for 25 h whereupon the corresponding dihydropyridine (**3f**) was obtained in 79% yield while the usual Hantzsch procedure afforded it in 39% yield (reflux for 24 h). In a similar manner, various *o*-substituted benzaldehydes were treated with ethyl

[1] For recent reviews, see:
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