486 **RESEARCH PAPER** JULY, 486–487 JOURNAL OF CHEMICAL RESEARCH 2004

Potassium fluoride/alumina mediated simple synthesis of Hantzsch 1, 4-dihydropyridines

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A general and practical technique to achieve synthesis of 1,4-dihydropyridines in excellent yields has been investigated using potassium fluoride/alumina (KF/Al_2O_3) as a solid base. The ammonia was obtained either from thermal decomposition of ammonium acetate or by passing ammonia gases in the form of bubbled through hetereogenous reaction medium using an apparatus.

Keywords: acetlyacetone**,** ethyl acetoacetate, 1,4-dihydropyridines, potassium fluoride/alumina, Hantzsch reaction

The use of potassium fluoride/alumina as a heterogeneous catalyst for various organic reactions are well known.[1] Recently, potassium fluoride/alumina has been used in both solid phase organic synthesis and with solid supported reagents.[2-3] The present study synthesises 1,4-dihydropyridines by a new and efficient method. For a number of years, derivatives of 1, 4-dihydropyridine have been synthesised by many different synthetic methods.[4-6] Especially in recent years, synthesis of substituted 1,4-dihydropyridines and pyridines have become very popular.[7] The preparation of 1,4-dihydropyridines by the classical Hantzsch synthesis a one-pot condensation of an aldehyde with an alkyl acetoacetate and ammonia was developed in 1882.[8] Khadilkar e*t al*. also described the formation, in a domestic oven, of 1,4-dihydropyridines in an aqueous hydrotropic solution (50% butylmonoglycolsulphate).[9] Gowravaram e*t al*. used TMSCl as a catalyst at room temperature.[10] Jhillu and Yavad have investigated the use of urea on the surface of silica gel under microwave irradiation in solvent free conditions for Hantzsch 1,4-dihydropyridines reactions.[11] More recently, Mohammed Ali Zolfigol e*t al*. have synthesised 1,4-dihydropyridines under solvent-free conditions at 80°C.[12] Hantzsch 1,4-dihydropyridines (1,4-DHPs) are well known as Ca^{2+} channel blockers, and have emerged as one of the most important classes of drugs for the treatment of cardiovascular diseases, including hypertension.[13-14]

We now describe a new procedure, the use of potassium fluoride/alumina, to promote the Hantzsch reaction. In the first procedure, to a suspension of potassium fluoride/alumina and ammonium acetate in acetonitrile were added aldehyde and ethyl acetoacetate or acetlyacetone. The reaction mixture was heated until acetonitrile started to reflux. The progress of the reaction was monitored by TLC. After completion of the reaction potassium fluoride/alumina was filtered off. The solvent was evaporated under reduced pressure and the crude product was separated by extraction and purified by crystallisation.

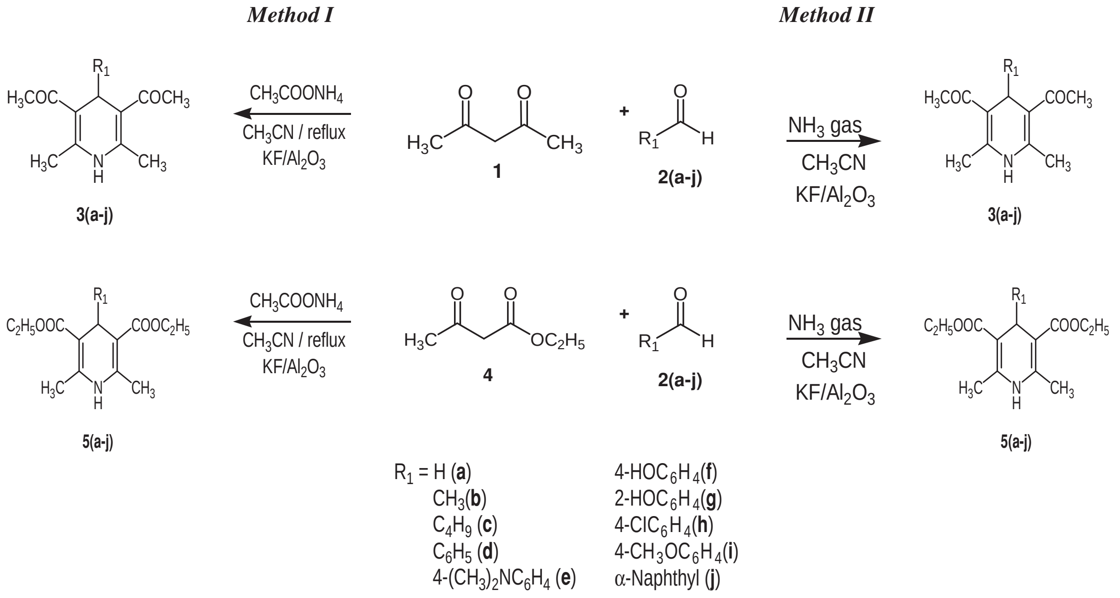
The second method was carried out at room temperature as described above. Ammonia gas was used instead of ammonium acetate. Ammonia was continously bubbled through the reaction apparatus during the reaction and the products were then isolated as described above.

Potassium fluoride/alumina mediated synthesis of 1, 4-dihydropyridines is short and efficient, and is an alternative method to synthesis of substituted 1,4-dihydropyridine derivatives.

Experimental

General procedure for the synthesis of 1,4-dihydropyridines

Method I: Acetylacetone **1** (4 g, 40 mmol), aldehyde (20 mmol), (Table 1–2 , **2a–j**) and CH_3COONH_4 (2.3 g, 30 mmol) were dissolved in acetonitrile (15 ml). This mixture was added on potassium fluoride/alumina (5 g) and was refluxed. The progress of the reaction



Scheme 1 General method for synthesis of 1,4-dihydropyridines.

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Table 1 Formation of 1.4-dihydropyridines by condensation over potassium fluoride/alumina of acetylacetone(**1**) with a variety of aldehyde and ammonia

		CH_3COONH_4 (*Method I*)		NH_3 [a] (gas) (*Method II*)	
Product **3a–j**	R_1 **2a–j**	Time/h	Yield/%	Time/h	Yield/%
a	H	3	90	2	89
b	CH_3	3	94	2	85
c	C_4H_9	4	89	2	79
d	C_6H_5	4	86	2	80
e	$4\text{-}(CH_3)_2NC_6H_4$	2.5	87	2	77
f	$2\text{-}HOC_6H_4$	2	84	2	84
g	$4\text{-}HOC_6H_4$	2	87	2	81
h	$4\text{-}ClC_6H_4$	3	86	2	74
i	$4\text{-}CH_3OC_6H_4$	2	88	2	85
j	α-Naphthyl	4	80	2	76

Acetylacetone(**1**) (40 mmol), aldehyde (20 mmol), ammonium acetate (30 mmol), potassium fluoride/alumina (5 g), acetonitrile (15 ml). All 1,4-dihydropyridines were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures. Potassium fluoride/alumina was prepared according to literature[15].

[a]Room temperature.

was monitored by TLC analysis. After completion of the reaction, the resulting suspension was filtered and the solid was washed with 10 ml acetonitrile. The solvent was evaporated and residue was washed with water and extracted in DCM (3 × 5 ml). The solution of DCM was dried with anhydrous $MgSO_4$. After removal of the DCM the product was crystallised from ethyl alcohol, (Table 1, **3a–j**). In a similar manner reactions were carried out with ethyl acetoacetate **4** (5.2 g, 40 mmol), (Table 2, **5a–j**).

Method II: Acetylacetone **1** (4 g, 40 mmol) and aldehyde (20 mmol) (Table 1,2 **2a–j**) were dissolved in acetonitrile (15 ml). This mixture was added on potassium fluoride/alumina (5 g) and ammonia gas was used continously bubbled through the reaction apparatus during reaction time at room temperature. The progress of the reaction was monitored by TLC analysis. After completion of the reaction, the resulting suspension was filtered and the solid was washed with 10 ml acetonitrile. The solvent was evaporated and residue was washed with water and extracted in DCM (3 × 5 ml). The solution of DCM was dried with anhydrous $MgSO_4$. After removal of the DCM the product was crystallised from ethyl alcohol, (Table 1, **3a–j**). In a similar manner reactions were carried out with ethyl acetoacetate **4** (5.2 g, 40 mmol), (Table 2, **5a–j**).

We are thankful to Mersin University Research Foundation for financial support of this work.

Received 10 May 2004; accepted 29 June 2004
Paper 04/2517

Table 2 Formation of 1.4-dihydropyridines by condensation over potassium fluoride/alumina of ethyl acetoacetate(**4**) with a variety of aldehyde and ammonia

		CH_3COONH_4 (*Method I*)		NH_3 [a] (gas) (*Method II*)	
Product **5a–j**	R_1 **2a–j**	Time/h	Yield/%	Time/h	Yield/%
a	H	3	87	2	86
b	CH_3	3	91	2	84
c	C_4H_9	4	86	2	74
d	C_6H_5	4	84	2	75
e	$4\text{-}(CH_3)_2NC_6H_4$	2.5	88	2	78
f	$2\text{-}HOC_6H_4$	2	82	2	89
g	$4\text{-}HOC_6H_4$	2	86	2	86
h	$4\text{-}ClC_6H_4$	3	90	2	70
i	$4\text{-}CH_3OC_6H_4$	2	88	2	85
j	α-Naphthyl	4	77	2	73

Ethyl acetoacetate(**4**) (40 mmol), aldehyde (20 mmol), ammonium acetate (30 mmol), potassium fluoride/alumina (5 g), acetonitrile (15 ml). All 1,4-dihydropyridines were characterised by comparison of their spectroscopic and physical data with authentic samples synthesised by reported procedures. Potassium fluoride/alumina was prepared according to literature[15].

[a]Room temperature.

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