

SYNTHESIS OF SOME NEW 3-ARYL-1-(4,6-DIMETHYL-2-PYRIMIDINYL)-4-FORMYLPYRAZOLES USING VILSMEIER HAACK REACTION

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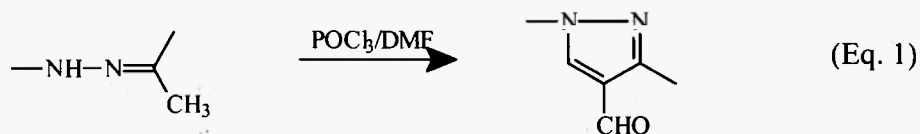
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Abstract :

Synthesis of some new 3-aryl-1-(4,6-dimethyl-2-pyrimidinyl)-4-formylpyrazoles has been accomplished by the reaction of 4,6-dimethyl-2-pyrimidinylhydrazones of various acetophenones with Vilsmeier – Haack reagent (POCl_3/DMF).

Introduction :

The use of Vilsmeier – Haack reagent (POCl_3/DMF) to bring about formylation and related transformations from aromatic and conjugated cyclic compounds is well established.¹ Besides this, the reagent is also employed for effecting various chemical transformations from other classes of compounds.² A notable example that finds an interesting and significant application in heterocyclic chemistry is the synthesis of pyrazoles from the reaction of hydrazones and semicarbazones with Vilsmeier reagent (Eq.1).³

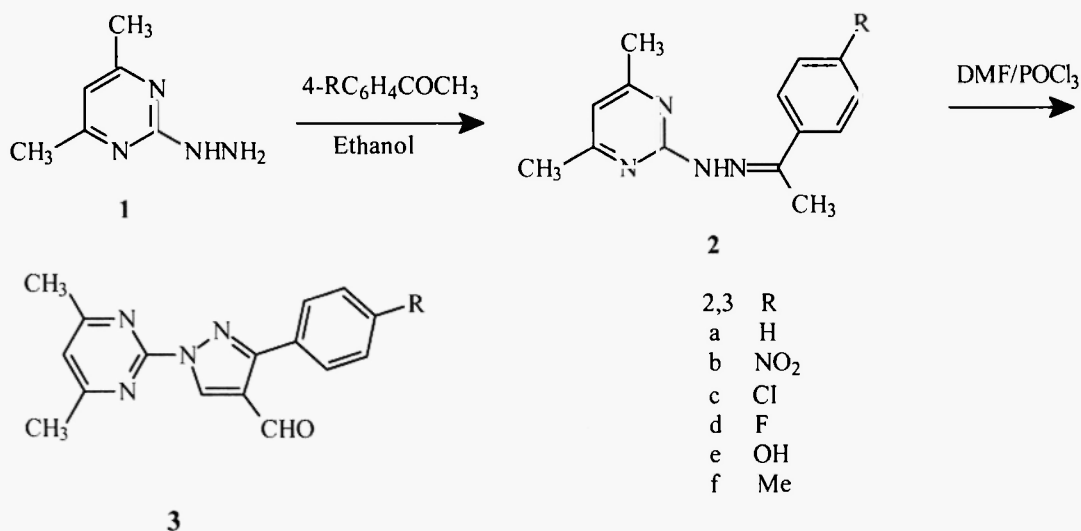


The wide range of biological activities such as antibacterial⁴, antifungal⁵ etc. associated with pyrazoles⁶ and pyrimidines⁷, coupled with the fact that much attention has not been paid to study the scope of this important modification of Vilsmeier reaction for the synthesis of pyrazole derivatives containing heterocyclic moieties⁸ such as pyrimidines etc., prompted us to undertake the synthesis of some new pyrimidinylpyrazoles (3a-3f) by using POCl_3/DMF .

Results and Discussion :

To check the feasibility of this approach for the synthesis of pyrimidinylpyrazoles, 4,6-dimethyl-2-pyrimidinylhydrazone (**2a**) of acetophenone was stirred with 3 equivalents of phosphorous oxychloride in DMF at a temperature of 50° –60° C for 2 hours. The reaction afforded the desired product 3-phenyl-1-(4,6-dimethyl-2-pyrimidinyl)-4-formylpyrazole (**3a**) in 65% yield.

The method was found to be general as hydrazones **2b-2f** of variously substituted acetophenones were converted to the corresponding pyrimidinylpyrazoles (**3b-3f**) in yields ranging from 65%-85% (Scheme 1) .The structures of the products were confirmed by their IR, ¹HNMR and HRMS data . The results of the reaction along with the chacterisation data are summazied in table 1.

**Scheme-1**

The new pyrimidinylpyrazoles (**3a-3f**) obtained from this study are important precursors for fused bis-pyrazoles. The synthesis of the latter involving hypervalent iodine reagents are under progress and will be published in detail in our future communications.

Experimental:

Melting points were recorded in open capillaries and are uncorrected. The ¹H NMR spectra of the products were recorded on Bruker spectrophotometer at 300MHz.

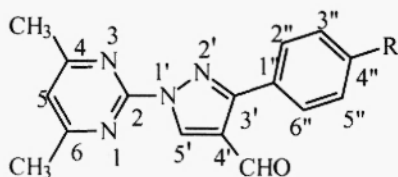
The requisite 4,6-dimethyl-2-pyrimidinylhydrazones (**2a-2f**) were prepared by the standard procedure involving condensation of 4,6-dimethyl-2-hydrazinopyrimidine (**1**) with corresponding acetophenones in ethanol.⁹ 4,6-Dimethyl-2-hydrazinopyrimidine (**1**) was synthesized according to the literature procedure commencing with urea and acetylacetone.¹⁰

Preparation of 3-aryl-1-(4,6-dimethyl-2-pyrimidinyl)-4-formylpyrazoles (3a-3f) :-

General Procedure:- To the Vilsmeier-Haack reagent prepared by dissolving POCl₃ (3 mmol, 0.28 ml) in 20-30 ml DMF appropriate hydrazone **2** (1mmol) was added and the reaction mixture was stirred at 50⁰-60⁰ C for a period of 2-3 hours. The reaction mixture was then poured over ice cold water. The solid that separated on neutralization with NaHCO₃ was filtered, washed with water and recrystallised from EtOH to afford pure 3-aryl-1-(4,6-dimethyl-2-pyrimidinyl)-4-formylpyrazole **3** (Table 1).

Antibacterial testing:

All the compounds (3a-3f) were tested against two organisms: *Staphylococcus aureus* (gram – positive) and *Pseudomonas aeruginosa* (gram – negative) at concentration of 5% in chloroform by Filter Paper Disk Method.¹¹ Both of the organisms were cultured in nutrient agar medium. However, none of the compounds showed any significant activity.

Table 1: Spectral and Physical data of **3****3**

Sr. No.	Compd.	M.Pt. (°C)	Yield (%)	IR(KBr) max., cm ⁻¹ .	¹ H NMR (CDCl ₃) (ppm)	HRMS (m/z) (M ⁺ , %)
1.	3a	120-121	65	1694	2.59 (s,6H, C ₄ -CH ₃ , C ₆ -CH ₃), 7.04 (s,1H,C ₅ -H), 7.46-7.50 (m,3H), 7.65-7.68 (m,2H), 9.26 (s,1H,C ₅ -H), 10.07 (s,1H,-CHO)	278.1165 (100)
2.	3b	145-146	83	1692	2.62 (s,6H,CH ₄ CH ₃), 7.09 (s,1H,C ₅ -H), 6.19-6.22 (d,2H,C ₂ -H,C ₆ -H), 6.32-6.35 (d,2H,C ₃ -H,C ₅ -H), 9.32 (s,1H,C ₅ -H), 10.1 (s,1H,-CHO)	323.1017 (80)
3.	3c	150-151	80	1692	2.60 (s,6H,C ₄ -CH ₃), 7.05 (s,1H,C ₅ -H), 7.44-7.47 (d,2H,C ₂ -H,C ₆ -H), 7.87-7.90 (d,2H,C ₃ -H,C ₅ -H), 9.27 (s,1H,C ₅ -H), 10.05 (s,1H,-CHO)	312.0770 (100)
4.	3d	100-101	77	1691	2.60 (s,6H,C ₄ -CH ₃), 7.06 (s,1H,C ₅ -H), 7.17-7.20 (d,2H,C ₂ -H,C ₆ -H), 7.91-7.94 (d,2H,C ₃ -H,C ₅ -H), 9.20 (s,1H,C ₅ -H), 10.05 (s,1H,-CHO)	296.1077 (100)
5.	3e	248-249	71	1699	2.59 (s,6H,C ₄ -CH ₃), 7.03 (s,1H,C ₅ -H), 7.70-7.93 (d,2H,C ₂ -H,C ₆ -H), 6.90-6.93 (d,2H,C ₃ -H,C ₅ -H), 9.24 (s,1H,C ₅ -H), 10.04 (s,1H,-CHO)	294.1110 (100)
6.	3f	151-152	68	1679	2.42 (s,3H,C ₄ -CH ₃), 2.59 (s,6H,C ₄ -CH ₃), 7.04 (s,1H,C ₅ -H), 7.75-7.77 (d,2H,C ₂ -H,C ₆ -H), 7.28-7.30 (d,2H,C ₃ -H,C ₅ -H), 9.27 (s,1H,C ₅ -H), 10.06 (s,1H,-CHO)	292.1569 (9.7)

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