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Synthetic Utility of Vilsmeier Reagents: Formation of Vinamidinium Salts from Acyl Ureas

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Abstract: Attempted synthesis of uracil derivatives (**2**) from acyl ureas (**1**) resulted in the formation of vinamidinium salts (**3**) which can be hydrolysed to give dialdehydes.

The Vilsmeier-Haack-Arnold reagent is extensively used for the formylation of activated aromatic compounds and carbonyl compounds.[1] Most of them describe an *ad hoc* procedure for the facile synthesis of aldehydes. A number of heterocycles have also been prepared using this reaction.[2] Vinamidinium salts obtained by using chloromethyleniminium salts have been exploited for the synthesis of condensed ring systems.[3] Recently, some interesting cyclisation reactions using Vilsmeier reagent have been reported from this laboratory.[4-6] In pursuance of our interest in Vilsmeier reagents together with a search for new pathways to synthesise various biologically active compounds, we have been exploring new and simple routes to substituted uracils, widely occurring component of nucleic acid used in biochemical research[7a] and 2-thio uracils, a substance with potent biological especially antithyroid activity.[7b]

In this Letter we report our observation on the action of chloromethyleniminium salt **4** derived from $POCl_3$ - DMF *in situ* against active methylene groups of N-acetyl urea, N-acetyl thiourea, phenylacetyl urea / thiourea, *p*-nitro-, *p*-bromophenylacetyl ureas and thioureas[8] in an attempt to synthesise corresponding uracil derivatives (Scheme 1 and Table 1).

Scheme 1

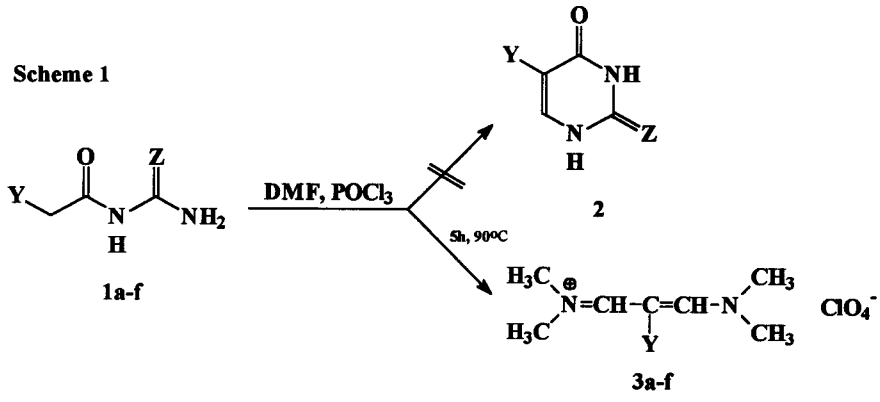


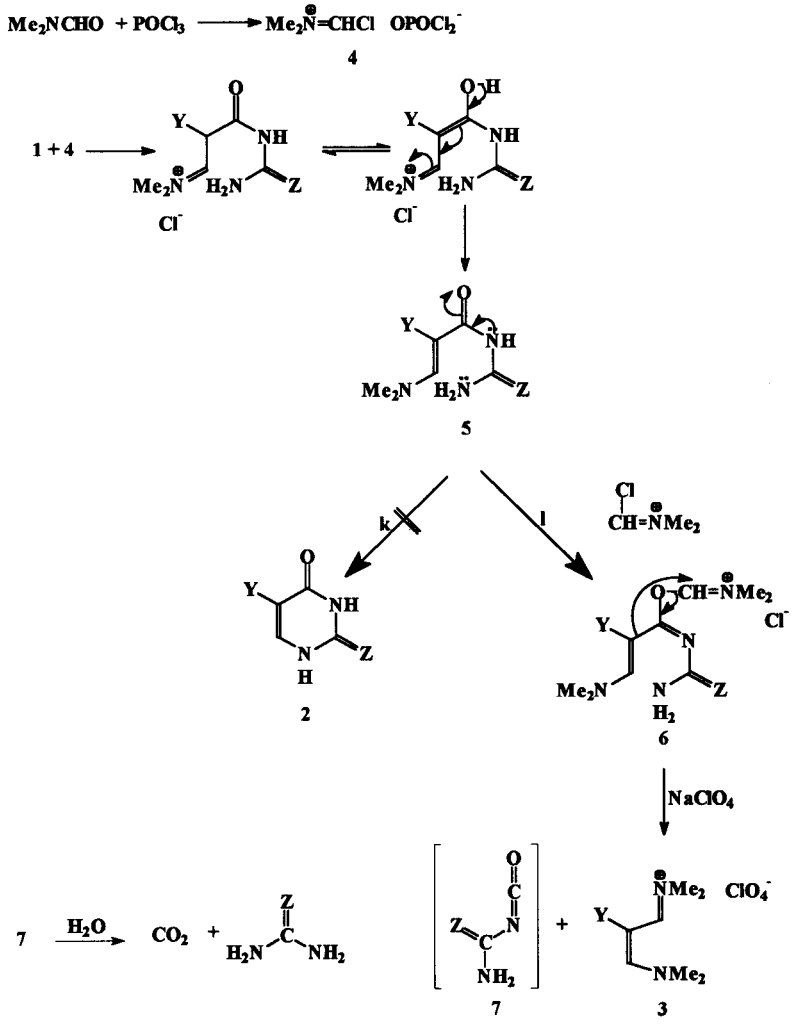
Table 1

Entry	Substrates		Product	Yield	Mp
	Y	Z	(Y)	(%)	(°C)
a	C_6H_5	O	C_6H_5	80	198
b	*p*-Br C_6H_4	O	*p*-Br C_6H_4	78	120
c	*p*-NO_2 C_6H_4	O	*p*-NO_2 C_6H_4	76	226
d	H	O	H	0	–
e	C_6H_5	S	C_6H_5	85	198
f	*p*-NO_2 C_6H_4	S	*p*-NO_2 C_6H_4	69	226

:All compounds gave satisfactory spectral data.

Contrary to our expectation a dialdehyde-yielding intermediate of vinamidinium salt **3** was obtained in each case. Literature survey reveals that vinamidinium salts have been prepared from arylacetic acids and Arnold[9] has suggested a mechanism for product formation through ketene intermediate YCH=C=O. In addition to several possibilities, the mechanism proposed in this paper, however appears far and away to be a better fit for this reaction. The mono formylated product **5** may undergo a second formylation at oxygen under the given condition[10] taking route 'l' rather than giving the expected product **2** which would have been possible by route '**k**'. The vinamidinium salts were obtained in very good yields and the impetus may be that the hypothetical isocyanate intermediate **7** gets easily expelled. This intermediate **7** being less stable gets decomposed during workup into CO_2 and urea, thus making urea as the apparent fragmenting group. A possible mechanism proposed for this reaction is given in Scheme **2**.

Scheme 2



Thus this paper describes a simpler method for obtaining several substituted β-dialdehyde precursors, which can be subsequently hydrolysed to corresponding dialdehydes by treatment with alkali. Further work is in progress in order to achieve the expected uracil derivatives as well as to prove the mechanism for the formation of **3** as given in Scheme **2**. The results of which will be communicated separately in the near future.

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10. **Typical experimental procedure:**

    1.78g (0.01 mole) of phenylacetyl urea **1a**[8] was dissolved in 8 mL DMF and kept in ice cold condition. To this 2.8 mL $POCl_3$ was added dropwise with stirring for 15 min. The reaction mixture was heated over water bath for about 5 hrs. Then the contents were poured into 100 g of crushed ice and treated with sodium perchlorate. The solid immediately formed was filtered, washed with water and dried at vacuum. The product upon recrystalisation using chloroform-petroleum ether yielded **3a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42(s, 6H, NMe_2), 3.45(s, 6H, NMe_2), 7.33(m, 5H, ArH), 7.82(s, 2H,=CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 40.2, 50.4, 107.7, 123.2, 127.5, 164.8; IR (KBr) : 1660, 1450, 1100 cm^{-1}; MS(m/e): 203(M^+).

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