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The Vilsmeier Cyclization of Azides. Synthesis of Oxazoles and Vinyl Azides from 2-Azidoacetophenones.

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Abstract: The synthesis of 5-aryloxazole-4-carboxaldehydes was accomplished by an unprecedented Vilsmeier cyclization of 2-azidoacetophenones. One-pot synthesis of these oxazolecarboxaldehydes from 2-bromoacetophenones by dehaloazidation- Vilsmeier cyclization reaction sequence provided better yields. The treatment of 2-azidoacetophenones with Vilsmeier reagent (DMF/$POCl_3$) at rt resulted in the exclusive formation of α-azido-β-chlorovinyl azides in moderate yields. © 1997 Elsevier Science Ltd.

The halomethyleniminium salts which are the reactive intermediates involved in the Vilsmeier-Haack-Arnold reaction are extensively used for the formylation of carbonyl compounds[1] and activated aromatic substrates.[2] The mild reaction conditions employed, commercial viability of the reagents and improved understanding of the reaction mechanisms ensure Vilsmeier reagents ever-increasing role in the construction of many heterocyclic systems.[3] Recently, our group has been focusing attention on exploiting the cyclization potential of halomethyleniminium salts for developing new synthetic strategies towards various nitrogen based heterocycles such as indoles, quinolines, quniazolinones and N-formyl lactams.[4]

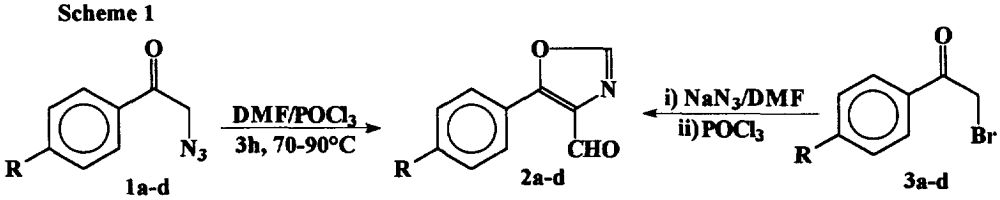
There is a current rapid increase in interest in the area of application of azides in organic synthesis owing to the high reactivity of azide function which is susceptible to photolysis, pyrolysis, cycloadditions and attack by nucleophiles as well as by electrophiles.[5] Stereoselective synthesis, metal-assisted azide decomposition applied to the synthesis of natural products and reductive cyclization are some areas of particular attention in which use of azides is rapidly gaining ground.[6]

The Vilsmeier reaction of an azido group which is strategically positioned from other active functional groups would seem to offer a unique opportunity for the construction of nitrogen based heterocyclic systems. This prompted us to investigate some of the general principles underlying the synthetic design of oxazole carboxaldehydes from the corresponding phenacyl azides as outlined in Scheme 1.[7]

The novelty of the process lies in the Vilsmeier cyclization of the azido group, which, to the best of our knowledge is unprecedented. The synthesis of 5-aryloxazole-4-carboxaldehydes was accomplished by the treatment of corresponding 2-azidoacetophenones (5 mmol) with 3 equivalents of Vilsmeier reagent at 80-90°C for 2-3 h in 3 mL of DMF. The prerequisite azidoacetophenones necessary for oxazole synthesis were prepared in essentially quantitative yields from the corresponding 2-bromoacetophenones. The conversion was carried out in DMF using 2 equivalent of NaN_3 at ambient temperatures for 10-20 min.

To further illustrate the scope and utility of the Vilsmeier cyclization, we examined a one-pot synthetic strategy of oxazolecarboxaldehydes directly from 2-bromoacetophenones. This dehaloazidation-Vilsmeier cyclization protocol was prompted by the facile conversion of bromoacetophenones to azidoacetophenones under mild conditions in DMF. Thus, to an ice-cooled, stirred solution of substituted 2-bromoacetophenone (5 mmol) in 10 mL of DMF, 1.1 equivalent of NaN_3 was added in one portion and after 10-20 min, 6 equivalent of

Scheme 1



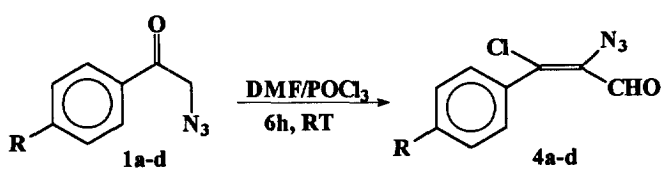
Entry	Product	R	Time of heating (h)	Yield(%)[a]	Mp (°C)
1	**2a**	Me	4	45	90
2	**2b**	Cl	4.5	48	130
3	**2c**	Br	4.5	56	135
4	**2d**	Ph	6	61	160

[a] :The values represent the isolated yields based on the preparation from **3a-d.**

$POCl_3$ was added dropwise. The mixture was allowed to attain room temperature and then maintained at 90°C for 4-6 h to give the corresponding oxazole-4-carboxaldehyde in good yield.

As some azido compounds are reported to be sensitive towards strong mineral acids, the reaction conditions were pursued with caution, keeping in mind, the release of hydrochloric acid inherently associated with the chloroformylation of carbonyl group. But surprisingly, the azide group exhibited remarkable resistivity towards Vilsmeier reagent at temperatures below 60°C and exclusive formation of α-azido-β-chlorovinyl aldehydes, a previously unreported class of vinyl azides, was achieved at room temperature using 6 equivalent of Vilsmeier reagent (Scheme 2).[7] The chemical manipulation of various functional groups in the presence of azido group is a field of current interest.[8]

Scheme 2

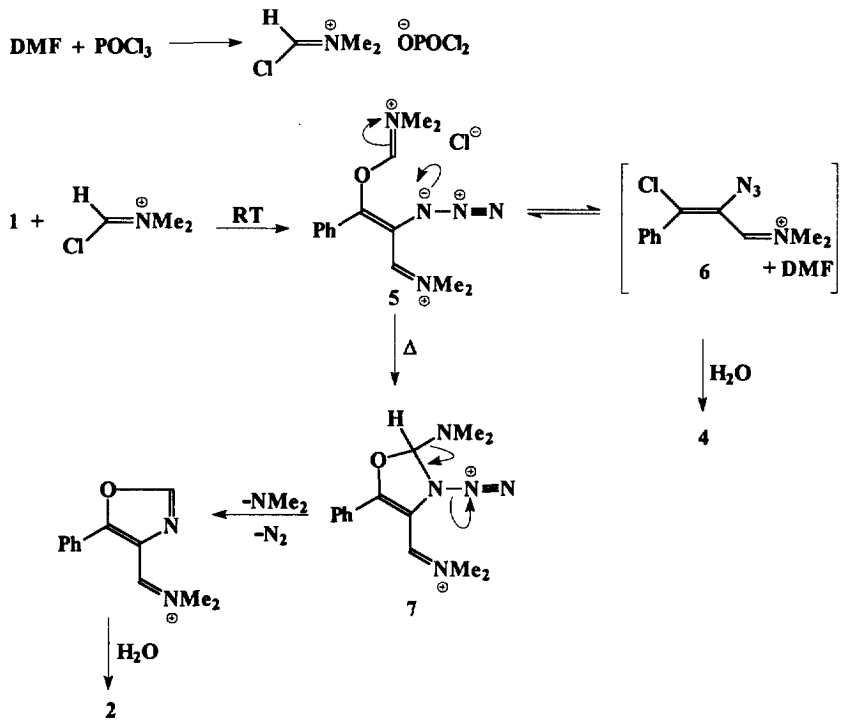


Entry	Product	R	Yield(%)	Mp(°C)
1	**4a**	Me	70	70
2	**4b**	Cl	62	98
3	**4c**	Br	65	104
4	**4d**	Ph	80	103

Thermal decomposition of vinyl azides for the synthesis of variety of heterocyclic systems including aziridines, nitrogen bridge head compounds and indoles has been developed into a powerful synthetic method.[9] However, very few efficient general methods are available for the synthesis of vinyl azides and most of the thermal or photochemical cyclizations have been carried out with azidocinnamates.[10] The susceptibility of carbonyl group to undergo chloroformylation under Vilsmeier conditions at room temperature without affecting the azide functionality, provides an attractive scheme for the synthesis of vinyl azides directly from phenacyl azides. These vinyl azides could be stored infinitely without any apparent sign of decomposition when maintained at 0-5°C. The preliminary study on the thermolysis of **4** indicates the formation of corresponding indoles.

Based on the above findings a plausible mechanism could be proposed for the Vilsmeier cyclization of azides (Scheme 3). The chloromethyleniminium salt generated form DMF and $POCl_3$ reacts with the carbonyl group of **1** to yield **5** which is in equilibrium with chlorovinyl azide precursor **6** . The reaction at rt followed by aqueous workup yields the vinyl azide **4**. At 80-90°C the reaction proceeds through the intramolecular nucleophilic attack of the iminium species by azide to yield the intermediate **7** which is followed by elimination of dimethylamino group and subsequent loss of nitrogen to give the corresponding oxazole **2**.

Scheme 3



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7. All the compounds gave satisfactory spectral data and elemental analyses.
   Representative spectral data:
   5-(4-Chlorophenyl)oxazole-4-carboxaldehyde(2b): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.98(s, 1H, CHO), 8.31(s, 1H), 8.00(m, 2H, Ar-H), 7.42(m, 2H, Ar-H);^{13}C NMR (75 MHz, $CDCl_3$): δ 183.6, 162.3, 144.2, 141.6, 137.5, 129.0, 127.9, 124.3; MS(m/e): 207(M^+); IR (KBr) : 3087, 2842, 1696, 1118 cm^{-1}.
   2-Azido-3-chloro-3-(4-chlorophenyl)-2-propenal(4b): ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.38(s, 1H, CHO), 7.42(m, 2H, Ar-H), 7.35(m, 2H, Ar-H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 183.9, 139.7, 137.4, 135.1, 132.0, 131.6, 129.1 ; MS(m/e): 213(M-28); IR (KBr) : 2110, 1676, 1432 cm^{-1}.
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