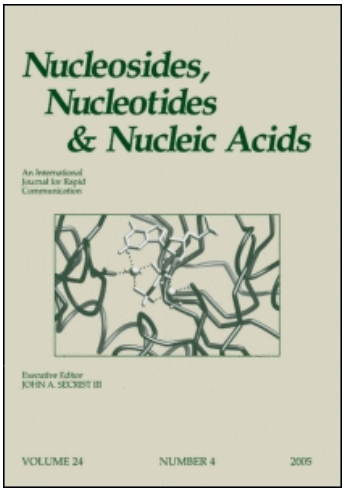

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Recent Advances in the Synthesis of 6-Vinyl-N,N-Dialkylcytosine Derivatives

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RECENT ADVANCES IN THE SYNTHESIS OF 6-VINYL-N,N-DIALKYLCYTOSINE DERIVATIVES

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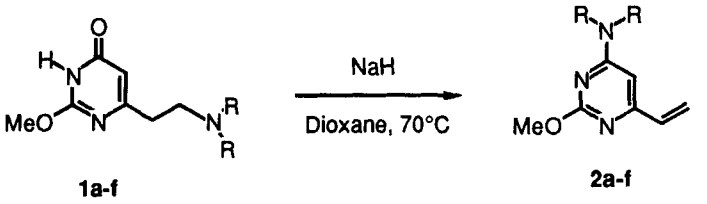
ABSTRACT: A general, selective and efficient synthesis of N,N-dialkyl-cytosine derivatives bearing a vinyl moiety on the C-6 side chain is reported.

Despite the fact that 2-, 4-, and 6-positions of pyrimidines are prone to direct nucleophilic attack, relatively few examples of direct removal of hydroxy (oxo) substituents are recorded. The aminolysis of 4(3H)-pyrimidinones with the introduction of secondary or tertiary amino groups in place of the 4-hydroxy group is possible only using appropriate phosphoramides as reagents at very high temperatures, ranging from 200°C to 300°C.[1] It is evident that both substrate and product must be exceptionally thermostable for this reaction to be practical. We have recentely reported[2] that 2-methoxy- and 2-methylthio-4(3H)-pyrimidinones bearing a diethylamino moiety on the C-6 side chain afford an unexpected and efficient direct nucleophilic C-4 hydroxy substitution when treated with dry alcoholic solutions of sodium alkoxides prepared from Na. An unprecedent tandem C-6 side chain Hofmann-like elimination/C-4 pyrimidinone substitution was also observed, as a competitive process, when sodium alkoxides prepared from alcohols and NaH in dioxane were used. We report here a new procedure for the one-pot selective and efficient synthesis of N,N-dialkyl-cytosine derivatives bearing a vinyl moiety on the C-6 side chain.

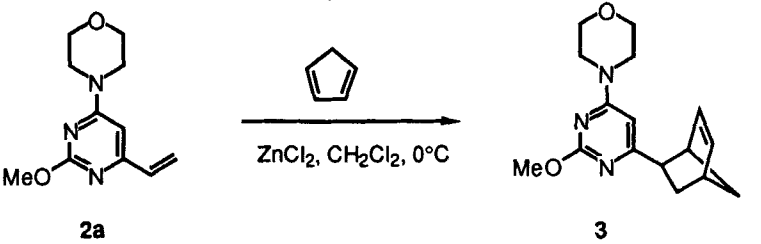
6-Vinyl-N,N-dialkyl-cytosine derivatives **2a-f** were prepared (in yields ranging from 25% to 74%) starting from easily available[2] 6-substituted 4(3H)-pyrimidinone derivatives **1a-f** by treatment with an excess of NaH (1.5 equiv) in dry dioxane at 70°C. Under these experimental conditions the tandem C-6 side chain Hofmann-like elimination/C-4 pyrimidinone substitution was the only observed process (FIG. 1). On the basis of

FIG. 1



a: R= $-CH_2CH_2OCH_2CH_2-$; **b** R= $-CH_2CH_2CH_2CH_2-$;**c**: R= $-CH_2(CH_2)_2CH_2CH_2-$;
d: R= $-CH_2(CH_2)_3CH_2CH_2-$;**e**: R= $-CH_2CH_2NHCH_2CH_2-$; **f**: R=$-CH_2(CH_2)_3CH_2CH_3$

FIG. 2



molecular models, we can exclude an intramolecular process for the formation of compounds **2a-f**, forbidden because of structural considerations. On the other hand, when the reactions were performed in the presence of 6-methyl-2-methoxy-4(3H)-pyrimidinone or methyl benzoate as scavengers of the dialkylamino or heterocyclic nucleophile, compounds **2a-f** were obtained without traces of cross-reaction products, showing that an intermolecular concerted process is operative. The ring size and the steric hindrance of the amino migrating group appears to control the efficiency of the process. In fact, the yields of compounds **2a-f** decreased when larger amino substituent are present on the C-6 side chain of substrates. Compound **2a-f** readily undergo Diels-Alder reactions with dienes. As an example, the reaction of **2a** (1 mmol) with an excess of cyclopentadiene (2.0 mmol) in CH_2Cl_2 at 0°C in the presence of catalytic amount of $ZnCl_2$ gave the *endo* 6-norbornene cytosine derivative **3** in high yield (83%) (FIG. 2). The stereochemical assignments of the *endo* configuration for **3** was performed by NOESY spectroscopy. This synthetic method open up a new route to N,N-disubstituted cytosine derivatives carrying a variety of substituents in the 6-position.

REFERENCES

1. Brown, D.J. "The chemistry of heterocyclic compounds", Vol. 16, Weissberger, Interscience, N.Y., **1962**.
2. Botta, M.; Occhionero, F.; Saladino, R.; Crestini, C.; Nicoletti, R. *Tetrahedron Lett.*, **1997**, 38, 8249-8252.