Alkylation of 1-(3,4-Disubstituted Phenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4(3*H*)-ones

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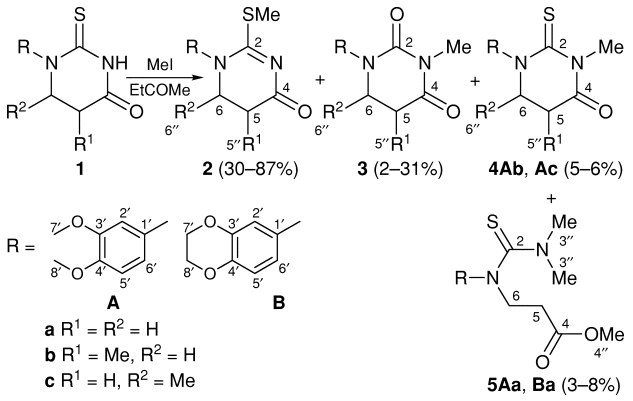
The results of a comprehensive investigation of the alkylation of the title compounds with MeI in butanone in the presence of K_2CO_3 are presented.

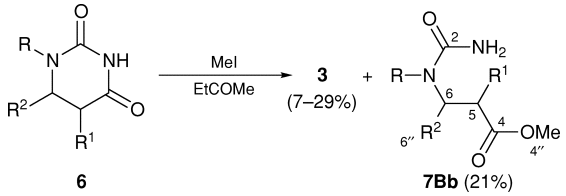
Dihydropyrimidinediones and dihydropyrimidinonethiones are known to be biologically active. Dihydropyrimidinonethiones, as well as dihydropyrimidinediones, being cyclic imides, exist as tautomers. Depending on the reaction conditions, electrophilic substitution can take place at the imide nitrogen or on the sulfur atom.[5,6] Desulfurization was reported to occur during alkylation of 1-phenyl-2-thioxo-1,2,5,6-tetrahydropyrimidin-4(3*H*)-ones.[7] However, proof of the structure of the only reported product was based solely on elemental analysis data.



Scheme 1

Alkylation of 1-(3,4-dimethoxyphenyl)- and 1-(3,4-ethylenedioxyphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4(3*H*)-ones and their 5- and 6-methyl homologues (**1**) with methyl iodide in butanone in the presence of an excess of K_2CO_3 resulted in the formation of a number of compounds. *S*- And *N*-methylated derivatives were formed in all alkylations (Scheme 1). The *S*-methylated products **2** were always the major products. In all cases methylation at the N(3) atom was also accompanied by desulfurization giving compounds **3**. To identify unambiguously the *N*(3)-methylated and desulfurized derivatives, they were synthesized independently by alkylation of 1-(3,4-dimethoxyphenyl)- and 1-(3,4-ethylenedioxyphenyl)-5,6-dihydro-2,4-(1*H*,3*H*)-pyrimidinediones and their 5- and 6-methyl homologues **6** under the conditions used for alkylation of thiones (Scheme 2). In addition to the products of desulfurization, 3,5-dimethyl- (**4Ab**) and 3,6-dimethyl-1-(3,4-dimethoxyphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4(3*H*)-ones (**4Ac**) were obtained in small quantities from the alkylation of **1Ab** and **1Ac**.

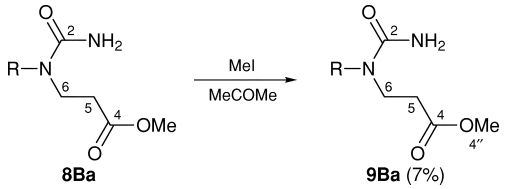
Small amounts of dimethylthiocarbamoyl derivatives **5** and the methyl ester of *N*-carbamoyl-*β*-alanine **7Bb** were separated from the reaction mixtures. They were identified



Scheme 2

as products of cleavage of the heterocyclic ring, followed by esterification and alkylation of the formed ureido and thioureido acids. Only *N*-alkylated thio derivatives were separated from the reaction mixtures. Dihydropyrimidinediones and their 2-thio analogues are known to cleave to form salts of the corresponding *N*-carbamoyl- and *N*-thiocarbamoyl-*β*-alanines on treatment with nucleophiles.[8,12] Thus, the basic medium of the alkylation and moisture present during the reaction was sufficient to facilitate such a cleavage of the heterocyclic pyrimidine ring. We suppose also that desulfurization occurred owing to moisture present in the reaction mixture. When dihydropyrimidine-2-thione **1Ab** was alkylated under strictly anhydrous conditions, traces of desulfurization and pyrimidine ring cleavage products were not noticed on a TLC plate.

To verify the structures of compounds **5** and **7Bb** and prove that such alkylation of the ureido and thioureido acids was possible, *N*-carbamoyl- **8Ba** and *N*-thiocarbamoyl-*β*-alanines **10Ba** were alkylated with methyl iodide. Methyl ester **9Ba** was obtained from the alkylation of **8Ba** (Scheme 3); only esterification took place as with **7Bb**. Alkylation of **10Ba** occurred both at oxygen and nitrogen to give the methyl ester of *N*-dimethylthiocarbamoyl-*β*-alanine **5Ba** (Scheme 4). Along with alkylation of thioureido acid, cyclization and desulfurization followed by alkylation occurred and **3Ba** and **4Ba** were obtained.



Scheme 3

The structures of the compounds were elucidated using ^1H and, especially, ^{13}C NMR spectroscopy as well as mass spectrometry. ^{13}C NMR spectroscopy is one of the most powerful techniques for the structural elucidation of these compounds, as a recent assignment of the ^{13}C resonances of a series of dihydrouracil and thiodihydrouracil derivatives has shown.[8,9]

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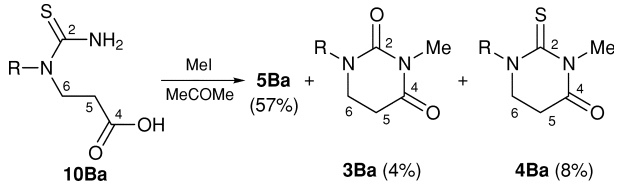

Scheme 4

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Techniques used: ^{1}H and ^{13}C NMR and mass spectrometry

References: 12

Schemes: 4

Table 1: ^{1}H NMR spectral data for compounds **2**

Table 2: ^{1}H NMR spectral data for compounds **3** and **4**

Table 3: ^{13}C NMR chemical shifts of compounds **2**–**5**, **7** and **9**

Table 4: Elemental analysis data

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