Alkylation of Non-electron Rich Nitrogen Heterocycles by Alkyl Orthoformates: Quantum Chemistry Calculations

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Results of semiempirical MO calculations of N_1- and N_2-alkyl pyrazolotriazolopyrimidin-4-ones originating from alkylation by trimethyl and triethyl orthoformate are presented.

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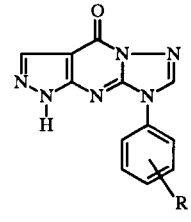
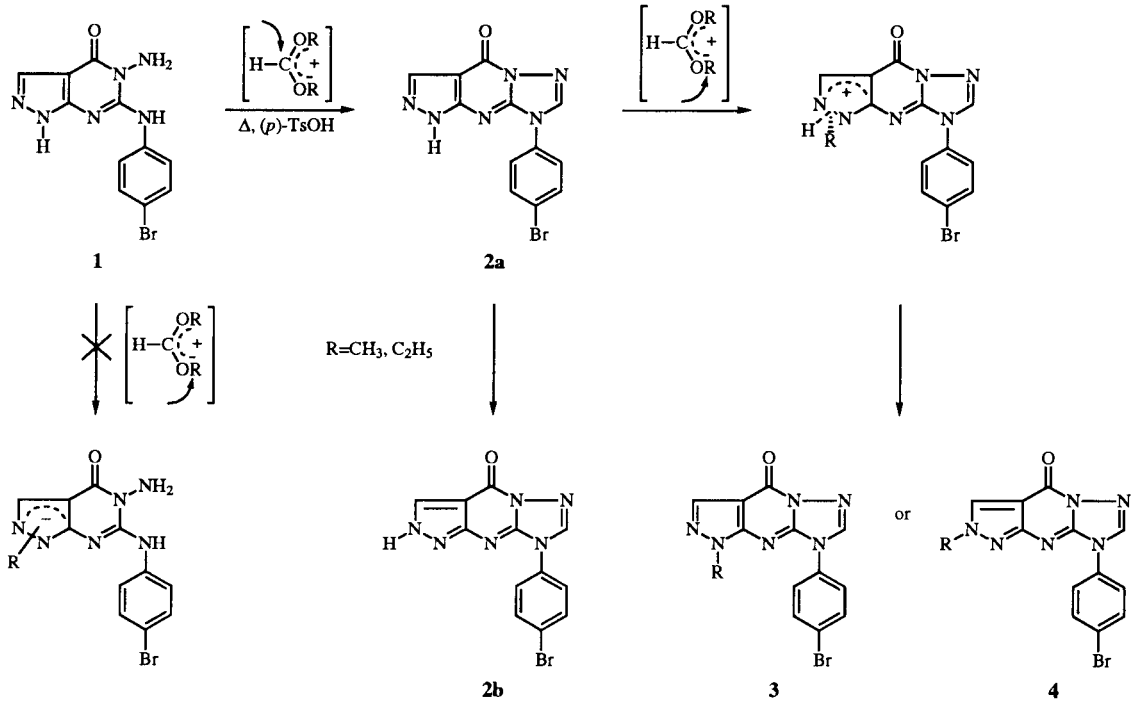
In connection with studies aimed at the synthesis of pyrazolotriazolopyrimidin-4-one derivatives of pharmaceutical interest (Formula **A**) the final formation of the condensed triazole ring using triethyl orthoformate as the C7 supplying agent constantly produced a byproduct having mass at M+ 28 with respect to the expected product [1,2]. The structural characterization of this impurity as the 2-ethyl 8-(4-bromophenyl)pyrazolo[3,4-*d*][1,2,4]-8*H*-triazolo-[2,3-*a*]-4*H*-pyrimidin-4-one (**4b**) led us to survey the potential of the unexpected reaction as a new *N*-alkylation method of non electron rich nitrogen heterocycles [3].



A

In fact, *N*-alkylation of an NH group is usually brought about by the action of either methyl iodide or dimethyl sulphate on the anion of the heterocycle, and this is sometimes conveniently achieved by the use of phase transfer conditions [4]. Although ortho esters and the di- and trialkoxycarbenium ions generated *in situ* from them by

Scheme 1
Reaction mechanism in the alkylating effect of trimethyl of triethyl orthoformate



1 **2a** **2b** **3** **4**

proton or Lewis acids action may constitute one of the longest and best studied class of the reactive intermediates in organic chemistry [5-9, 11], little is known of their potential as alkylating agents, particularly in the area of the non electron rich nitrogen heterocycles [12,13]. The ortho esters chemistry was recently presented in an exhaustive review by Pindur [11]. We believed it valuable to perform a thorough investigation in order to establish the more appropriate conditions at which the reaction occurs in an advantageous and specific way also comparing the effect of other ortho esters [6-9]. In this paper the results of attempts to further rationalize the unexpected reaction using semiempirical molecular orbital (MO) calculations are presented.

A reaction mechanism for the alkylating effect of trimethyl or triethyl orthoformate on pyrazolopyrimidinone **1** has recently been proposed by us [2] (Scheme 1). This pathway is supported by the findings of the now performed theoretical investigations (results of all calculations are listed in Table 1). From homo/lumo energy comparison (following the frontier molecular orbital concept [10]) as well as from atom partial charge estimation (see Figure 1) it is obvious that the first attack of a carbenium ion is likely to take place at the NH_2 or at the NH group thus leading to the condensed triazolo system, **2a,b**. After this initial step both pyrazole nitrogen atoms are susceptible for an alkylation reaction as can be deduced from the homo energies and charge distribution (Figure 2). As can be seen from both AM1 and PM3 calculations, the N_1-H tautomeric form **2a** is energetically favored compared to

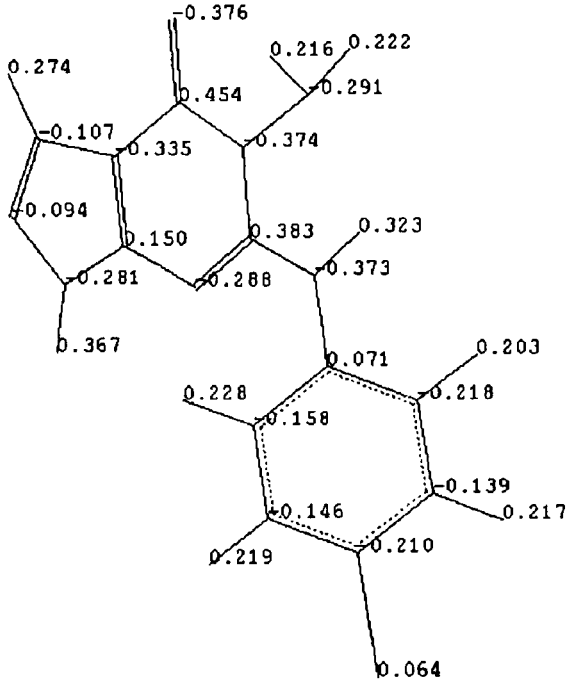


Figure 1. Mulliken population on AM1 optimized structure of **1**.

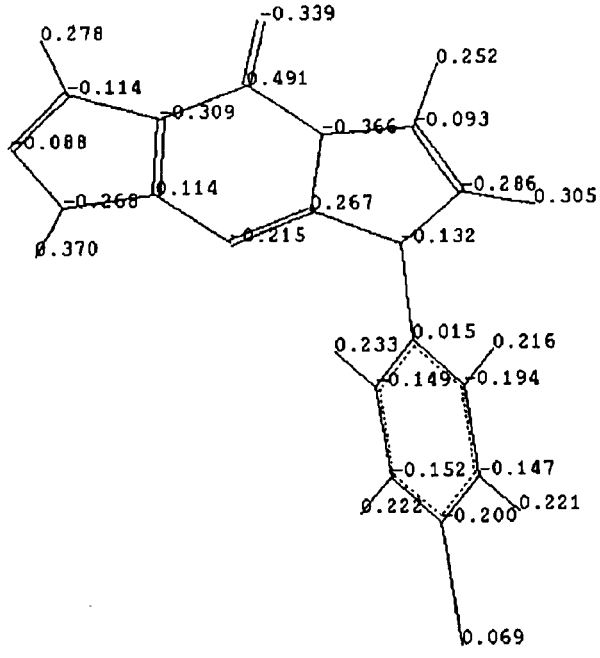


Figure 2. Mulliken population on AM1 optimized structure of **2a**.

the N_2-H tautomer **2b**. Moreover, from comparison of ΔH_f both N_1 alkyl derivatives **3** are thermodynamically more stable (*ca.* 3-3.5 kcal/mol, depending upon the hamiltonian used) than the N_2 substituted isomers **4**. This is in agreement with the experimental findings [2] that the N_2 ethyl derivative **4b** is only formed when high reaction temperatures are applied. On the other hand, a mixture of N_1 and N_2 ethyl derivatives **3b**, **4b** is obtained upon reaction at lower temperature and the N_1 isomer **3a** is being exclusively formed when trimethyl orthoformate is used. In general, the SN_2 transfer of a

Table 1

Results from Semiempirical MO Calculations

Compound	method [a]	ΔHf [b]	homo [c]	lumo [d]
1	AM1	259.8678	-8.9558	-0.6601
	PM3	87.5339	-8.9426	-0.7060
2a	AM1	192.7633	-9.3104	-4.4863
	PM3	124.1214	-9.0017	-4.2691
2b	AM1	196.4537	-9.2131	-4.3007
	PM3	124.1346	-8.9395	-4.1681
3a	AM1	198.6058	-9.2108	-4.4435
	PM3	117.8792	-9.0646	-4.2829
3b	AM1	191.7392	-9.1683	-4.4233
	PM3	113.2754	-9.0478	-4.2641
4a	AM1	201.8748	-9.1087	-4.2602
	PM3	121.8999	-8.9337	-4.0859
4b	AM1	195.6235	-9.0617	-4.2312
	PM3	115.7485	-8.9193	-4.0785

[a] Hamiltonian used. [b] Heat of formation (kcal/mol). [c] Energy of highest occupied molecule orbital (eV). [d] Energy of lowest unoccupied molecule orbital (eV).

methyl group in comparison with an ethyl group in the alkoxy carbenium ions is more easily feasible. In this case however, so far no N_2-methyl derivative could be recovered from the reaction mixture as a consequence of a decomposition process due either to the higher trimethyl orthoformate reactivity or instability of compound **4a**. These findings confirm that an important role is played by inverse thermodynamic stabilization effects of the N_1 or N_2 alkyl derivative and the NH tautomeric equilibrium of the pyrazole ring [4,12,14]. Further experiments will be carried out to exploit this study for defining the reaction conditions to obtain selectively N_1- or N_2-derivatives.

EXPERIMENTAL

All molecule structures were built within the Sybyl [15] molecular modeling software package installed on a SGI Indy 4400XZ or a SGI PowerChallenge XL starting from geometrically optimized standard fragments of the Tripos library. The potential energies of each structure were fully refined using the MM3 force field [16]. MO calculations were performed within the MOPAC [17] module using both the AM1 and the PM3 hamiltonian, geometries were fully optimized, and the keyword PRECISE was used. Charge densities were obtained by Mulliken population analysis [18].

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