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THE FREE RADICAL BROMINATION OF ETHYL PYRIDAZINES: THEORETICAL STUDIES.

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ABSTRACT

Theoretical studies on free radical bromination by N-bromosuccinimide were carried out on a range of ethyl-3-methoxy-pyridazine derivatives. The investigations of these reactions performed, in order to develop a convenient and rapid theoretical means of predicting selectivity. The geometry optimizations of the total energies of the reactants and the products were calculated using Semi empirical; AM1, MNDO, PM3 and Hartree Fock; HF3-21G computational methods. The calculation performed using PM3 Hamiltonian gave the best qualitative predictions, thus providing a rapid method for the selectivity of the reactions used in the synthesis of novel heterocyclic analogues of neurotransmitters.

KEY WORDS: Hartree Fock calculation; semi-empirical calculation; N-bromosuccinimide; pyridazines.

RESUMO

Foram efetuados estudos teóricos da bromação de derivados de etil-3-metoxipiridazinas com radicais livres usando N-bromosuccinimida. O propópsito principal dos estudos foi o desenvolvimento de métodos teóricos rápidos para predizer a seletividade. As otimizações geométricas dos reagentes e dos produtos foram calculadas usando os métodos computacionais semi-empíricos AM1, MNDO, PM3 e Hartree Fock, HF3-21G. Os cálculos efetuados usando o Hamiltoniano PM3 levaram às melhores previsões. Os resultados permitem prever a seletividade de reações usadas na síntese de compostos heterocíclicos novos que são análogos de neurotransmissores.

PALAVRAS CHAVES:

Cálculos Hartree Fock, Métodos Semi-Empíricos, N-Bromosuccinimida

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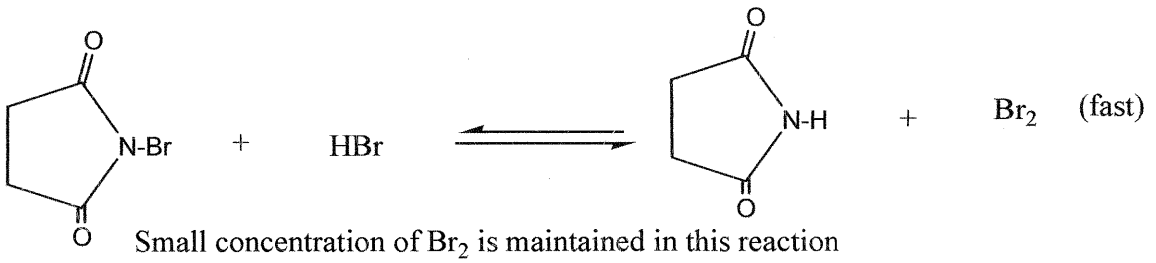
1. INTRODUCTION

Pyridazine and its derivatives were used in many research fields due to their structure ans reactivity to form stable yields with important biological properties [1] The Wohl-Ziegler bromination which is one of the most popular methods of obtaining **α**-alkyl arenes, is usually performed with N-bromosuccinimide (NBS) in the presence of a radical initiator at high temperature in solvent CCl4[2]. The major drawback of carbon tetrachloride as a solvent, however, is its toxicity, carcinogenicity and also its properties of ozone-layer damaging [3]. The reaction is believed to take place by free-radical mechanism [4], is generally conducted in carbon tetrachloride as solvent, and is catalyzed by light and peroxides. N-bromosuccinimide is used as a source of low concentration bromide, which produces bromine radical which initiates the reaction [5]

The rate limiting step is the formation of the aromatic methylene free-radical (see scheme 1)



Small concentration of Br_2 is maintained in this reaction

$Br_2 \rightleftharpoons 2Br^{\cdot}$ (fast)

$ArCH_3 + Br^{\cdot} \longrightarrow ArCH_2^{\cdot} + HBr$ (slow)

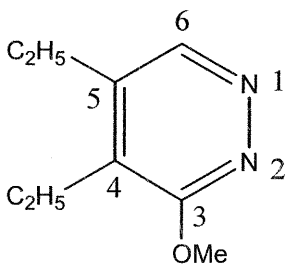
$ArCH_2^{\cdot} + Br_2 \longrightarrow ArCH_2Br + Br^{\cdot}$ (fast)

Scheme 1

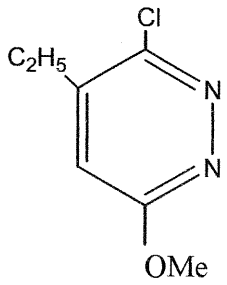
The more stable product will usually be the resonance- stabilized free-radical intermediate and the breaking of the carbon-hydrogen bond are crucial to the ease of bromination and the selectivity of the reaction, outweighing other factors such as steric effects.

The Wohl-Ziegler reaction has been used to produce intermediate for the synthesis of bioactive analogues of the neurotransmitters. In the course of the synthesis of such analogues, based on the pyridazine heterocycle, it has been found that this essential step is unreliable, unexpected products have been formed, and some compounds fail to brominates [6].

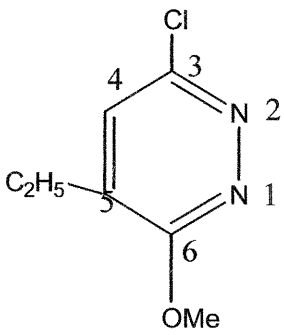
The aim of the study presented here is to develop a convenient and preferably rapid theoretical means of predicting selectivity of the products by predicting the total energies and heat of reactions.



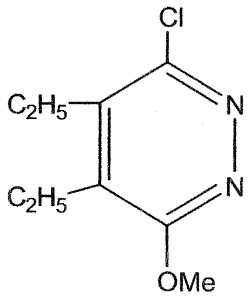
3-methoxy-4,5-dimethyl-pyridazine



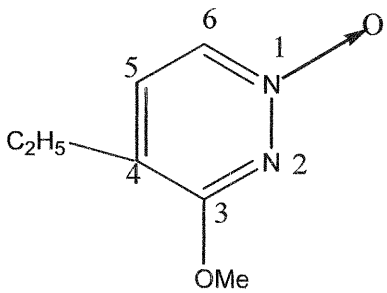
3-chloro-4-ethyl-6-methoxy-pyridazine.



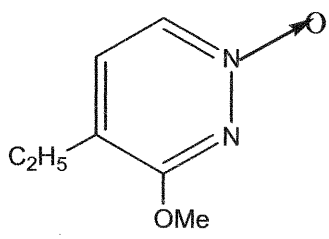
3-chloro-5-ethyl-6-methoxy-pyridazine



3-chloro-4,5-diethyl-6-methoxy-pyridazine



3-methoxy-4-ethyl-pyridazine-1-oxide



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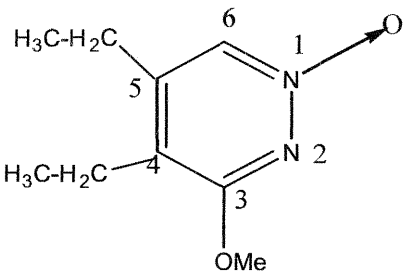

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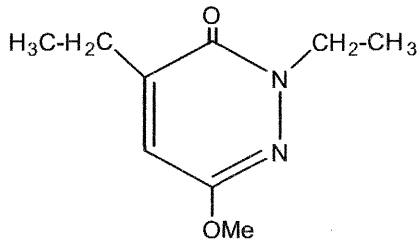
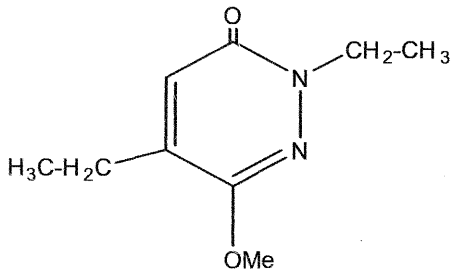
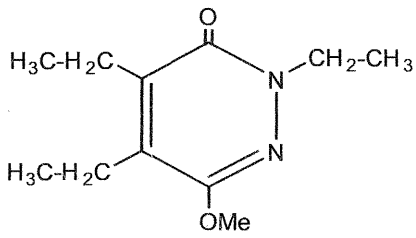


2,4-diethyl-6-methoxy-pyridazinone



2,5-diethyl-6-methoxy-pyridazinone



2,4,5-triethyl-6-methoxy-pyridazinone

Fig.1. The structures of the Ethyl-3-methoxy-pyridazine derivatives.

2. COMPUTATIONAL DETAILS

Theoretical studies were performed on ten (10) Ethyl-3-methoxy-pyridazine derivatives in order to investigate the best theoretical method in the in the synthesis of ethyl-3-methoxy-pyridazine derivatives. Geometry optimizations for these structures were carried out at semi-empirical MO methods; PM3, AM1, MNDO and Ab initio calculation H3-21G [7]. The molecular orbital's and the electronic structure were interpreted based on PM3, AM1, MNDO and Ab initio calculations. All quantum chemical calculations were performed using Spartan 10 program package.

3. RESULTS AND DISCUSSION

Table.1. List the relative energies of the heat of formation, H_f[RH] at various levels of theory.

S/N	PRODUCTS	AM1 (kJ/mol^{-1})	PM3 (kJ/mol^{-1})	HF 3-21 G (au)
	HBr	-43.94	22.42	-2560.84279
1	3-Methoxy-4,5-diethyl-pyridazine	-35.64	-42.08	-529.713823
2	3-Chloro-4-ethyl-6-methoxy-pyridazine	16.50	-13.16	-908.874745
3	3-Chloro-5-ethyl-6-methoxy-pyridazine	-3.89	-13.56	-908.891311
4	3-Chloro-4,5-diethyl-6-methoxy-pyridazine	-52.52	-66.47	-986.530383
5	3-methoxy-4-ethyl-pyridazine-1-oxide	91.22	-5.23	-526.429874
6	3-methoxy-5-ethyl-pyridazine-1-oxide	108.10	-9.75	-526.419201
7	3-methoxy-4,5-diethyl-pyridazine-1-oxide	38.66	-64.55	-604.073846
8	2,4-diethyl-6-methoxy-pyridazinone	-128.57	-192.35	-604.183992
9	2,5-diethyl-6-methoxy-pyridazinone	-130.48	-194.60	-604.180383
10	2,4,5-triethyl-6-methoxy-pyridazinone	-177.97	-252.74	-681.827061

Table.2. List of the total energies of pyridazine radicals, Included for reference is the same calculation on bromine.

S/N	PRODUCTS	AM1 (kJmol^{-1})	PM3 (kJmol^{-1})	HF 3-21G (au)
	Bromine radical	111.88	111.88	-2560.24462
1	3-Methoxy-4,5-diethyl-pyridazine radical	(R4)107.15	100.31	-529.078883
		(R5)107.10	95.35	-529.082634
2	3-Chloro-4-ethyl-6-methoxy-pyridazine radical	137.10	125.60	-908.243085
3	3-Chloro-5-ethyl-6-methoxy-pyridazine radical	133.91	124.94	-908.259073
4	3-Chloro-4,5-diethyl-6-methoxy-pyridazine radical	(R4)90.20	77.46	-985.899326
		(R5)85.57	72.28	-985.898886
5	3-methoxy-4-ethyl-pyridazine-1-oxide radical	220.08	129.20	-525.799422
6	3-methoxy-5-ethyl-pyridazine-1-oxide radical	239.33	128.59	-525.787475
7	3-methoxy-4,5-diethyl-pyridazine-1-oxide radical	(R4)166.41	85.06	-603.441975
		(R5)168.44	75.05	-603.442014
8	2,4-diethyl-6-methoxy-pyridazinone radical	(R2)18.01	-60.82	-603.550887
		(R4)7.39	-60.27	-603.551697
9	2,5-diethyl-6-methoxy-pyridazinone radical	(R2)17.53	-57.33	-603.547397
		(R5)9.35	-56.33	-603.549787
10	2,4,5-triethyl-6-methoxy-pyridazinone radical	(R2)-36.54	-115.51	-681.183088
		(R4)-39.54	-110.18	-681.195602
		(R5)-40.06	-104.46	-681.195763

R2-5: Indicates radical positions.

Table.3. List the heat of reaction, calculated by subs rating heat of formation of the parent species and bromine radicals from parent radicals and hydrogen bromide.

Heat of reaction (kJ/mol^{-1}), [$H_fR^{\cdot}$) + $H_f(HBr)$] - [(H_fRH) + ($H_fBr^{\cdot}$)]

S/N	PRODUCTS	AM1	PM3	HF 3-21G
1	3-Methoxy-4,5-diethyl-pyridazine			
	1(4)	-13.03	52.74	96.52
	1(5)	-13.08	47.78	86.67
2	3-Chloro-4-ethyl-6-methoxy-pyridazine			
	2(4)	-35.22	49.61	87.91
3	3-Chloro-5-ethyl-6-methoxy-pyridazine			
	3(5)	-18.02	48.93	89.43
4	3-Chloro-4,5-diethyl-6-methoxy-pyridazine			
	4(4)	-13.10	54.28	86.33
	4(5)	-17.73	49.10	87.48
5	3-methoxy-4-ethyl-pyridazine-1-oxide			
	5(4)	-26.96	44.78	84.74
6	3-methoxy-5-ethyl-pyridazine-1-oxide			
	6(5)	-24.59	48.69	88.08
7	3-methoxy-4,5-diethyl-pyridazine-1-oxide			
	7(4)	-28.07	59.96	88.47
	7(5)	-26.04	49.95	88.36
8	2,4-diethyl-6-methoxy-pyridazinone			
	8(2)	-9.24	41.88	91.70
	8(4)	-19.86	42.43	89.58
9	2,5-diethyl-6-methoxy-pyridazinone			
	9(2)	-7.81	47.62	91.39
	9(5)	-15.99	48.62	85.12
10	2,4,5-triethyl-6-methoxy-pyridazinone			
	10(2)	-14.78	47.58	120.23
	10(4)	-17.39	52.91	87.38
	10(5)	-17.91	36.40	86.96

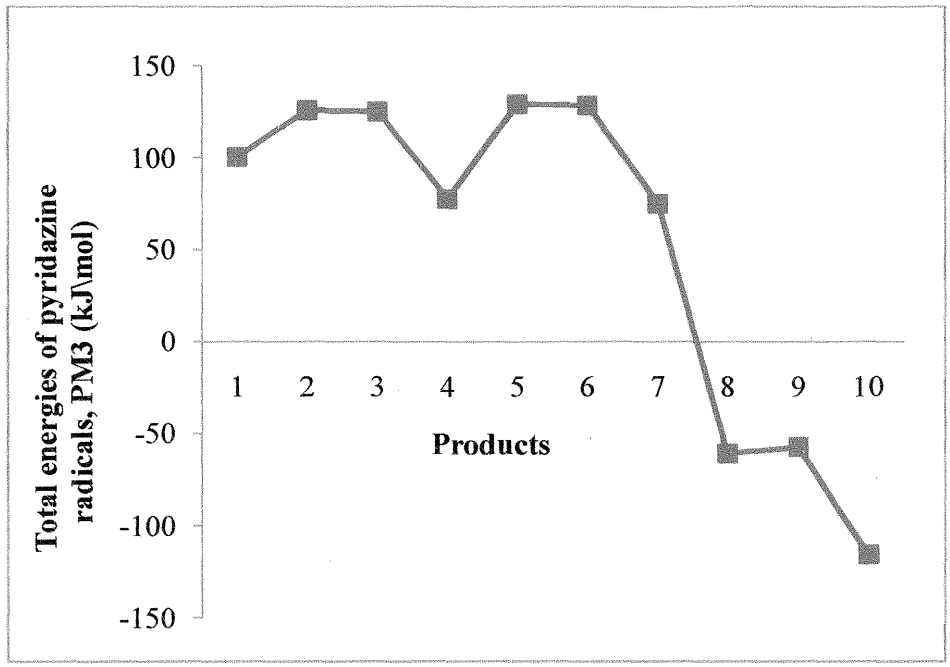


Fig.2. Correlation between the PM3 total energies of pyridazine radicals

From the table 3, the theoretical methods performed on the ethyl-3-methoxy-pyridazine derivatives predicted the greater stability of methylene radicals at the ortho verse us the metal position with a typical energy difference for reactions being around 1-20kj/mol to the methoxy substituent is consistently favoured. We find that the orders of heat of reaction values calculated from PM3 are in agreement with those obtained from ab initio results, but not in other semi empirical methods.

The most reliable semi empirical method, PM3 gave a larger heat of reaction for (7) 3-methoxy-pyridazine-1-oxide at the methylene radical at position 4 than for any others, although HF3-21G did not. The reaction (7) at the methylene radical at position 4 was found to be generally more unfavourable compared with the reaction (7) at the methylene at position 5. Since ring bromination has been observed in this case, it likely that the methylene radical at position 4 has sufficiently high energy for more favoured ring radical species to be produced, possibly involving rearrangement.

The theoretical methods performed on the N-ethyl-pyridazinones (8-10) were favoured 8(4),9(5) and 10(4) over 8(2),9(2) and 10(2) respectively, except PM3 rather favoured 8(2),9(2) and 10(2). The differences in energies observed particularly for HF3-21G, do not reflect the proportion of the N-bromoethyl product formed in this reaction. It can also be shown from fig 2, that total energies obtained from PM3 are the most satisfactory among the methods; this result is in agreement with that obtained by [8]

4. CONCLUSION

The free radical bromination of ethyl-3-methoxy-pyridazine derivatives through the wohl-zeigler reaction is found to be related to the stability of the free radicals formed in the rate limiting step. The semi empirical calculation using the PM3 Hamiltonian gave the most satisfactory results, hence, is the best method for predicting the selectivity of these reactions.

5. REFERENCES

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