



Research Article

Theoretical calculations of some new N-(α,β -Unsaturated acyl)sulfonamides and an investigation on correlations with those experimental values

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Abstract

Previously some new N-(α,β -Unsaturated acyl)sulfonamides are prepared (i) by the N-acylation of sulfonamides with N-(α,β -unsaturated acyl)benzotriazoles in the presence of potassium *tert*-butoxide and (ii) by reactions of appropriate α,β -unsaturated carboxamides with sulfonylbenzotriazoles in the presence of sodium hydride. The reaction efficiency has been changed related to route i or ii. Certain theoretical properties of N-(α,β -Unsaturated acyl)sulfonamides and reactants were calculated in Gaussian09 program using DFT method at B3LYP/6-311+g(d,p) level of theory. The theoretical data was then compared with certain experimental results.

Keywords: N-(α,β -unsaturated acyl)sulfonamides, DFT, Gaussian, experimental and theoretical correlation.

1. Introduction

N-(α,β -Unsaturated acyl)sulfonamides are plant disease control agents (Itsuki et al. 2005) selective EP₃ antagonists (Juteau et al. 2001; Belley et al. 2006) anti-inflammatory agents (Belley et al. 2006) and useful intermediates in asymmetric 1,4-addition (Chiacchio et al. 2002; Oppolzer et al. 1989; Nagashima et al.1985) for the synthesis of substituted β -lactams (Homsı & Rousseau 1999), γ -butyrolactams (Xu et al. 2006), and 2-quinolinones (Arisawa et al. 2005; Hajra et al. 2005).

Published preparations of N-(α,β -unsaturated acyl)sulfonamides include (i) the acylation of sulfonamides (RSO₂NH₂) by unsaturated acyl chlorides (R'CH=CHCOCl) in the presence of a base (such as triethylamine (Belley et al. 2006; Arisawa et al. 2005), *n*-butyllithium (Homsı & Rousseau 1999), or NaH (Knowles et al. 2000; Cheeseman & Varvounis 1988) or a copper powder catalyst (Heyboer & Staverman 1950); unsaturated carboxylic acids via mixed anhydride in the presence of Lewis acid catalyst (Reddy et al. 2007); (ii) reactions of aryl isocyanates (RSO₂NCO) with 1-alkenyltrialkylstannanes, di-1-alkenyl dibutylstannanes in the presence of aluminium trichloride (Niestroj et al. 1994) or with substituted alkenes (Lyutenko et al. 2003).

We reported the acylation of sulfonamides with stable, crystalline N-(α,β -unsaturated acyl)benzotriazoles to give N-(α,β -unsaturated acyl)sulfonamides (Katritzky et al. 2009). A general method for the preparation of N-(α,β -unsaturated acyl)sulfonamides from the corresponding sulfonamides by N-acylation with N-(α,β -unsaturated acyl)benzotriazoles were developed (Method A)(Scheme 1). The acylating agents, unsaturated N-acylbenzotriazoles, were prepared in 74–95% yield from the corresponding carboxylic acids and benzotriazole with thionyl chloride (Katritzky et al. 2005). Sulfonamides were prepared by the reaction of the corresponding sulfonyl chloride with ammonia (28% solution)(Hayashi et al. 2004).

Under the optimized conditions, N-(α,β -unsaturated acyl) sulfonamides were obtained in good yields (48-91%) from the reaction of a range of acylating agents and sulfonamides in the presence of a base (Method B) (Scheme 1).

With an alternative route we obtained N-(α,β -unsaturated acyl) sulfonamides. Sulfonylbenzotriazoles were prepared by the reaction of the corresponding α,β -unsaturated acid and benzotriazole with thionyl chloride. Reaction of α,β -unsaturated carboxamide with sulfonyl benzotriazoles in the presence of a base gave desired product in 30–71% yield (Katritzky et al. 2009). Experimental results showed that product was obtained in different efficiency and conditions such as temperature, base depending on reaction route.

In this article, certain series of reactions, molecules were chosen from our published article (Katritzky et al. 2009) to compare the efficiency of two routes theoretically. The study of 7 compounds, including β -Heteroarylacryloyl benzotriazoles, Sulfonamide, Sulfonylbenzotriazoles, α,β -unsaturated carboxamide as reactants and 3 N-(α,β -Unsaturated acyl)sulfonamide molecules as products is presented here. Theoretical properties of all molecules have been calculated in Gaussian09W software (Frisch et al. 2009) using DFT method at B3LYP/6-311+g(d, p) level of theory. The stability of molecules that contain carbonyl group has been investigated. Comparison of reaction tendency and molecular stability in two routes (Method A and Method B) was determined from calculated physicochemical parameters. Finally the agreement of calculated values with experimental results is discussed.

For this purpose values of dipole moment, atomic charge in nucleophiles and electrophiles and HOMO-LUMO of reactants have been studied. Finally the agreement of calculated values with experimental results is discussed.

2. Material and Method

2.1. Experimental Data Set

2.1.1. Method A

N-(α,β -unsaturated acyl)sulfonamides (**3**) were prepared reaction of N-acylbenzotriazoles (**1**) with sulfonamides (**2**) in the presence of potassium t-butoxide in THF (Table1) (Katritzky et al. 2009).

2.1.2. Method B

N-(α,β -unsaturated acyl)sulfonamides (**3**) were prepared reaction carbonyl amide (**4**) sulfonyl-benzotriazole (**5**) in the presence of NaH in THF (Table1)(Katritzky et al. 2009).

Scheme 1. Preparation of sulfonamides via Method A and Method B

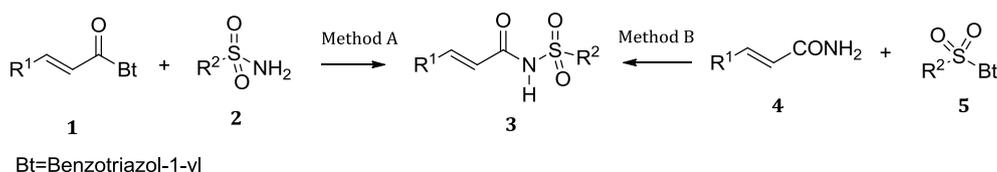


Table1. Preparation of N-(α,β -unsaturated acyl)sulfonamides

Entry	Compounds	Method	Yield ^b (%)
1	 1a 2a 3a	A	80
2	 1b 2a 3b	A	89
3	 1c 2a 3c	A	91
4	 4a 5a 3a	B	71
5	 4b 5a 3c	B	30

Method A: KOtBu/THF, 0 °C–r.t., Method B¹: NaH/THF, r.t., ^bIsolated yield.

2.1.3. Experimental Result

When (**1**) reacted with (**2**), desired products (**3**) were obtained in the presence potassium tert-butoxide at 0 °C to room temperature in good yield by Method A. Reaction of carbonyl amide (**4**) with sulfonyl-benzotriazoles (**5**) in the presence KOtBu (Potassium t-butoxide) failed to give product (**3**) (Method B). However, when reaction repeated in the presence of sodium hydride at room temperature gave the expected N-(α,β -unsaturated acyl)sulfonamide **3** (**3a** and **3c**) in lower yield. It has been required to compare theoretical calculation with these experimental results.

2.2. Calculation Methodology

2.2.1. Quantum Chemical Calculation

All of the molecular structures were constructed by using ChemDraw Ultra 12.0 (CS ChemBioDraw Ultra 12.0 2010). For every molecule, if it has more than one possible conformer, all conformers were optimized with MarvinView 14.7.7 program (Marvin Beans 2014). The conformer with the lowest electronic energy was used in this work.

The data for geometry optimization were estimated by molecular mechanic program (CS ChemOffice Ultra 12.0 for Microsoft windows); The structure was copied to Chem3D Ultra 12.0 to create 3-D model, and the model was subjected to energy minimization (Dewar et. al. 1985). The theoretical calculation was carried out by Gaussian09W software (Gaussian 09. Revision 2009). The molecular structures of 10 compounds in the ground state are optimized by using B3LYP method with 6-311+g(d,p) basis set (Foresman & Frisch 1996). The molecular properties were studied at DFT/rb3lyp/6-311+g(d,p) scrf=(cpcm,solvent=thf).

3. Result and Discussion

The physicochemical parameters; sum of electronic and Zero-point vibrational energy (ZPVE), sum of electronic and Thermal energy (TE), sum of electronic and Enthalpy (SE), sum of electronic and thermal Free Energy (SETFE) were calculated in Hartree/Particle unit for molecules and are summarized in Table 2.

Table 2. Calculated energies of the studied molecules in THF phases (DFT/rb3lyp/6-311+g(d,p))

Sum of electronic and Zero-point Energies (Hartree/ Particle)					Sum of electronic Thermal-Energies (Hartree/ Particle)					
Entry	Molecules			Bt	Reaction	Molecules			Bt	Reaction
1	1a	2a	3a	-395.875556	0.001183	1a	2a	3a	-395.869646	0.001241
	-817.656898	-875.514819	-1297.294978			-817.642226	-875.503770	-1297.275109		
2	1b	2a	3b	-395.875556	-0.001839	1b	2a	3b	-395.869646	-0.001949
	-815.472261	-875.514819	-1295.113363			-815.458493	-875.503770	-1295.094566		
3	1c	2a	3c	-395.875556	-0.001936	1c	2a	3c	-395.869646	-0.002873
	-1138.456398	-875.514819	-1618.097597			-1138.442099	-875.503770	-1618.079096		
4	4a	5a	3a	-395.875556	-0.001309	4a	5a	3a	-395.869646	-0.001514
	-478.346766	-1.214.822459	-1297.294978			-478.336732	-1.214.806509	-1297.275109		
5	4b	5a	3c	-395.875556	-0.009768	4b	5a	3c	-395.869646	-0.011046
	-799.140926	-1.214.822459	-1618.097597			-799.131187	-1.214.806509	-1618.079096		
Sum of electronic Enthalpies (Hartree/ Particle)					Sum of electronic thermal Free Energies (Hartree/ Particle)					ΔG
1	1a	2a	3a	-395.868702	0.001241	1a	2a	3a	-395.905667	0.000547
	-817.641282	-875.502826	-1297.274165			-817.700948	-875.552949	-1297.347683		
2	1b	2a	3b	-395.868702	-0.001948	1b	2a	3b	-395.905667	-0.001655
	-815.457549	-875.502826	-1295.093621			-815.51491	-875.552949	-1295.163847		
3	1c	2a	3c	-395.868702	-0.002873	1c	2a	3c	-395.905667	-0.000321
	-1138.441155	-875.502826	-1618.078152			-1138.500032	-875.552949	-1618.147635		
4	4a	5a	3a	-395.868702	-0.001514	4a	5a	3a	-395.905667	-0.001811
	-478.335788	-1.214.805565	-1297.274165			-478.383237	-1.214.868302	-1297.347683		
5	4b	5a	3c	-395.868702	-0.011047	4b	5a	3c	-395.905667	-0.007661
	-799.130242	-1.214.805565	-1618.078152			-799.177339	-1.214.868302	-1618.147635		

3.1. Theoretical Discussion

In Table 2, Reaction column shows the Energy Change Values of reaction. Free energy change of reaction is calculated by the formula:

$$\Delta G = \sum (G)_{\text{products}} - \sum (G)_{\text{reactants}},$$

and applied to other energies.

For Method A, the stability of 1a, 1b, 1c was observed in the same order for Zero-point vibrational Energies, Thermal Energies, Enthalpies and Free Energies as $1c > 1a > 1b$. The stability of 3a, 3b, 3c was observed in the same order for all energies as $3c > 3a > 3b$. If the energy change of reaction is considered, chemical change tends to occur in $3 > 2 > 1$ order shown with entry numbers except for Free Energies (Table 2). In Figure 1, The free energy change (ΔG) data of products related to Method A and B is shown.

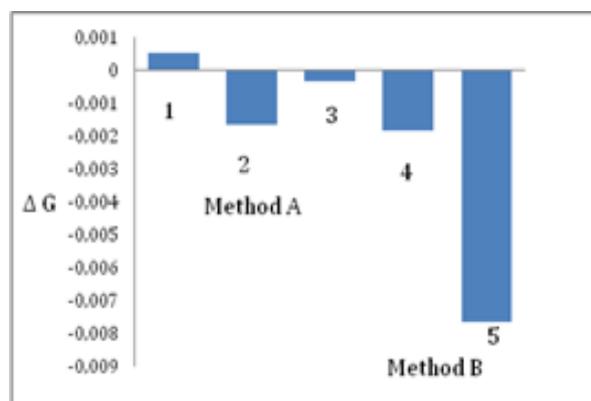


Figure 1. Free Energy Change Values of reactions 1, 2, 3, 4, 5.

For Method A, the reaction of ΔG is in $2 > 3 > 1$ order as demonstrated in Figure 1. For Method B, comparing the 2 reactions, the tendency occurs in order $5 > 4$ (Figure 1).

Comparing Method A with Method B, two pairs of reactions produce two same products. Reactions 1 and 4, 3 and 5 have been discussed. The result is as $4 > 1$ and $5 > 3$. Thus, the products synthesized with Method B are much more favorable. The order is $5 > 4 > 2 > 3 > 1$.

In the reactions given in Table 1; Nucleophiles 2a, 4a, 4b attack the substrates 1a, 1b, 1c, 5a and leaving group Benzotriazole (Bt) departs. In the assessment of electrophilicity of 1a, 1b, 1c, 5a; As the atoms C or S are attracting electrons, the charges of these have been compiled in Table 3.

Table 3. Mulliken atomic charges of electrophiles and nucleophiles

Electrophile	Mulliken Atomic Charge of Carbon		Nucleophile	Mulliken Atomic Charge of Nitrogen	
	Electrophile	Nucleophile		Electrophile	Nucleophile
	1a	2a	2a	-0.511	
	1b	-0.111			
	1c	-0.147			
	5a	0.403	4a	-0.432	
			4b	-0.430	

Electrophile strength has been determined as $5a > 1c > 1b > 1a$ according to the charges. Similarly for nucleophilicity discussion of 2a, 4a, 4b; since donating electrons, the charges of N shown in Table 3 were examined.

Nucleophile power is in the range of $2a > 4a > 4b$. The obtained results show that reactions are more favorable for Method B than Method A. The reaction tendency is in the order $5 > 4$ (Method B) $> 3 > 2 > 1$ (Method A) partly agreement with Free Energy Change (Figure 1).

Table 4 summarizes calculated dipole moments of all molecules. Dependence of total dipole moment data vs reactants is shown in Figure 2 and Figure 3. Reactant 5a which was used in Method B, has the most highest dipole moment. When comparing the reactions of 5a with 4a or 4b; 4b is more reactive than 4a due to the larger dipole moment. Therefore, the sequence $5 > 4 > 2 > 3 > 1$ is supported by Free Energies Range (Figure 1).

Table 4. Dipole moments of molecules

	Dipole Moment (Debye) (Field -independent basis)			
	X	Y	Z	Total
1a	-1.7633	-1.2039	0.0027	2.1351
1b	-3.0532	-1.7936	0.0039	3.5411
1c	2.6658	1.7786	0.0027	3.2047
5a	-3.2663	-7.2270	-2.2419	8.2416
2a	-4.6029	-0.0455	4.1555	6.2013
4a	1.8502	4.7770	0.0004	5.1228
4b	4.3997	-3.2964	1.7956	5.7834
3a	-3.8328	6.9195	3.4730	8.6388
3b	-4.4089	7.2403	-3.8590	9.3141
3c	4.2330	6.9248	-4.0066	9.0512

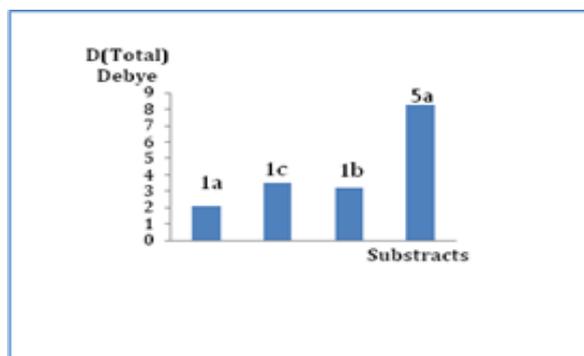


Figure 2. Dipole moment of substrates.

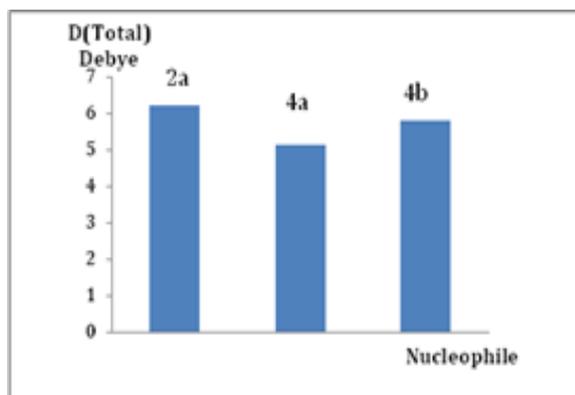


Figure 3. Dipole moment of nucleophiles.

Table 5 contains the data for HOMO (high occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) values of reactants and HOMO-LUMO gap for the reaction. High HOMO electrons are characteristic for nucleophiles therefore, the reactivity is written as $4b > 4a > 2a$ (Table 5). Molecules with the lower LUMO electron values has more electrophilicity, thus the reactivity of electrophiles in a $1c > 1a > 1b > 5a$ order. High HOMO and Low LUMO which means lower HOMO-LUMO gap mixing constitutes reactivity. In terms of HOMO-LUMO gap, favorable products tend to be in the reaction order of $5 > 4$ (Method B) $> 3 > 1 > 2$ (Method A). Again, in theory the reaction has a greater tendency to proceed in Method B than Method A.

Table 5. HOMO-LUMO values of reactants

Entry	HOMO (eV)	LUMO (eV)	HOMO -LUMO gap (eV)
1	2a -0.27060	1a -0.10219	0.16841
2	2a -0.27060	1b -0.10200	0.16860
3	2a -0.27060	1c -0.10352	0.16708
4	4a -0.24569	5a -0.07942	0.16627
5	4b -0.23541	5a -0.07942	0.15599

3.2. Theoretical and experimental agreement

Taking into consideration close values of yield for reactions by Method A (3, 91%; 2, 89%; 1, 80%, Table 1), the experimental yield values agree well with the energy changes given in Figure 4 and the Free energy change given in Figure 1.

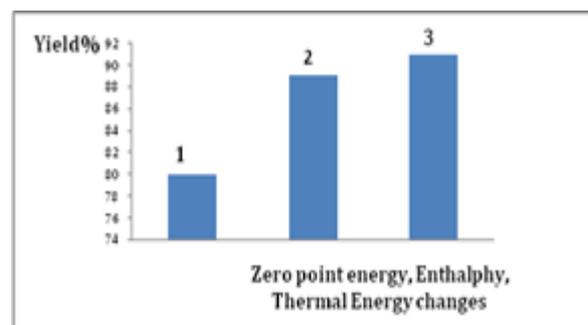


Figure 4. Energies change versus Yields

Theoretically, the reaction proceeded by Method B is more favorable than Method A for all types of energies in contrast to experimental data. Theoretical values of dipole moment, atomic charge in nucleophiles and electrophiles and HOMO-LUMO of reactant supported the result.

4. Conclusion

Theoretical calculation of 10 molecules was made from what we had already synthesized (Katritzky et al. 2009). Comparison of reaction tendency and molecular stability in two routes (Method A and Method B) was determined

from calculated physicochemical parameters. The structure stabilities of all molecules have been calculated by DFT and the results are compared with those of experimental ones.

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