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Regioselective aminoethylation of 1,4-benzodiazepin-2-one under conventional heating and microwave irradiation☆

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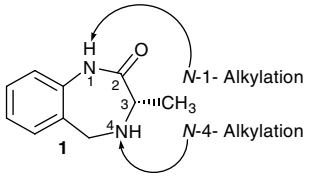
Abstract—The regioselective aminoethylation of 1,4-benzodiazepin-2-one **1** can be carried out using classical heating or microwave irradiation as the source of energy to furnish either *N*-1 or *N*-4 aminoethylated products **2a–d** and **3a–d**, respectively. The regioselectivity observed has been rationalized using computational studies and has been traced to the disparity of the rate-determining steps along the *N*-1 product (*N*-1 PR) and *N*-4 product (*N*-4 PR) formation pathways.

The new and quickly growing technique of microwave (MW) irradiation as a non-conventional sources of energy in synthetic organic chemistry has received a lot of attention in recent years.[1] The use of microwaves lead to a reduction in the amount of solvent, a decrease in reaction time, high yields, a reduction in side products, successful product formation in cases that fail under conventional conditions and an increase in the rate of chemoenzymatic reactions, etc.[2–6] Thus, MW irradiation has been used for a variety of organic reactions. However, the issue of stereo-, regio-, and chemoselectivity has not been addressed to a great extent.[4,7–9] In this paper, we report a regioselective aminoethylation of 1,4-benzodiazepin-2-one **1** both through classical heating and microwave irradiation as the sources of energy.

As part of our research program on the synthesis and biological activities of alkyl chain substituted 1,4-benzodiazepin-2-ones, we have already reported the synthesis of the pharmacophore **1**.[10] In connection with this work, we have synthesized *N*-1 and *N*-4 substituted benzodiazepin-2-ones regioselectively, by changing the mode of the energy source.

There are two reactive centers for aminoethylation in the 1,4-benzodiazepine skeleton **1**. The two nitrogens



have different environments and hence their reactivities are also different. This difference in reactivity was demonstrated by treating compound **1** with different aminoethylating agents. For example, when **1** was reacted with substituted chloroethylamine hydrochlorides in the presence of K_2CO_3 under conventional heating[11a] for nearly 6–8 h, exclusively *N*-1 substituted aminoethylated products **2a–d** were isolated. On the other hand, when the same reaction was carried out under microwave irradiation[11b] for 90 s, *N*-4 aminoethylated products **3a–d** were formed exclusively, Table 1. The two regioisomeric products were distinguished by their ^{1}H NMR spectra (200 MHz). The spectra of **2a–d** display the absence of a proton associated with *N*-1 at δ 8.34–8.73 ppm while the spectra of **3a–d** show the absence of a proton at *N*-4 at δ 1.87–2.14 ppm.

Possible routes for the formation of **2a–d** and **3a–d** are shown below (Schemes 1 and 2). The abstraction of a proton from the two nitrogen atoms of **1** generates two different types of anions. The −ve charge of the anion generated from *N*-1 is delocalized into the carbonyl group. Thus the *N*-1 center of **I** (Scheme 1) can be regarded as a soft anion center and is associated as loose

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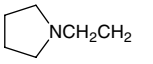
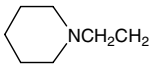
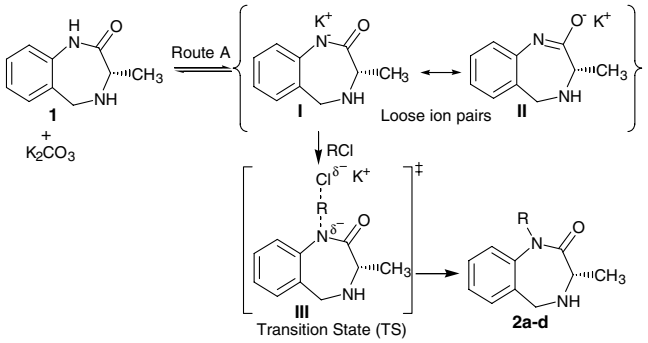
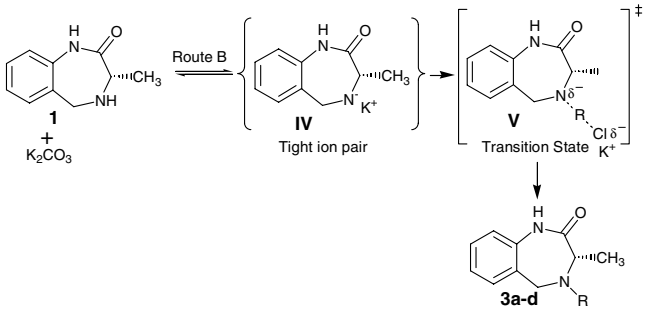
Table 1. Aminoethylation of 1,4-benzodiazepin-2-one **1** under conventional heating and microwave irradiation

Entry	R	Conditions	Product (%), physical state	Conditions	Product (%), physical state
1	$(CH_3)_2NCH_2CH_2$	K_2CO_3, DMF, 80 °C, 6 h	**2a** (65%), pale yellow semi-solid	K_2CO_3, DMF, MW, 90 s	**3a** (64%), brown semi-solid
2	$(CH_3CH_2)_2NCH_2CH_2$	K_2CO_3, DMF, 80 °C, 6 h	**2b** (76%), brown semi-solid	K_2CO_3, DMF, MW, 90 s	**3b** (72%), pale yellow semi-solid
3		K_2CO_3, DMF, 80 °C, 7 h	**2c** (76%), brown semi-solid	K_2CO_3, DMF, MW, 90 s	**3c** (67%), brown semi-solid
4		K_2CO_3, DMF, 80 °C, 8 h	**2d** (68%) brown semi-solid	K_2CO_3, DMF, MW, 90 s	**3d** (65%), brown semi-solid



Scheme 1. A possible reaction path for **2a**–**d** (Route A).



Scheme 2. A possible reaction path for **3a**–**d** (Route B).

ion pairs (**I** and **II**) with the K^+ ion. There is little change in polarity between the ground state (GS) and the transition state (TS) **III** and the reaction requires a small activation energy $\Delta G^{\#}$.[1c,12,13] Thus, *N*-1 aminoethylation is favored under conventional heating conditions via a S_N2 reaction involving the charge delocalized anion **III** and RCl to furnish **2a**–**d** (Scheme 1, Route A). Only weak specific microwave effects can be foreseen under these conditions.[1c,13]

It is generally accepted that MW effects increase when the polarity of the system is enhanced. As a consequence, specific microwave effects directly depend on the structure of reactive ion pairs. In route B, the anion **IV** generated by abstraction of a proton is localized due to the absence of any conjugation and can be regarded as a hard anion center with a high charge density; thus the reaction is concerned with tight ion pairs. During the course of the reaction, ion dissociation is increased and hence the polarity is enhanced from the GS toward the transition state **V** requiring higher activation energy $\Delta G^{\#}$.[1c,12–14] Specific microwave effects[1c] can therefore be seen at *N*-4. Thus, *N*-4 aminoethylation occurred through an anionic S_N2 reaction involving the charge localized anion **V** and RCl to furnish **3a**–**d** (Scheme 2, Route B).

Calculations were carried out to understand the observed regioselectivity. All the structures considered were optimized using the Hartree–Fock (HF/6-31G*) level of theory. To obtain reliable estimates of energy, single point energies were evaluated at the MP2/6-31G* level on HF/6-31G* geometries. In the discussion only MP2 energies are used unless otherwise specified. Quantitative values of energy are very much comparable at the HF and MP2 levels, indicating no significant sensitivity on the types of method used. However, dipole moment values are more sensitive, but importantly the trends are similar. Thus, the results obtained by computational studies are largely independent of the method of calculation. Irrespective of the alkyl group, the differences in dipole moment values from reactant **1** to *N*-1 transition state (TS_1) are consistently lower than the difference between **1** and the *N*-4 transition state (TS_2). In general the microwave conditions favor the reaction channels where the polarity of the system is enhanced along its route. Thus, the computational results account for the observed microwave effects on aminoethylation of benzodiazepin-2-one (**1**). All calculations were carried out using the Gaussian 03[15] suite of programs.

Figure 1 depicts the competing reaction profiles of the twin anionic species (*N*-1 and *N*-4) at the MP2/6-31G*//HF/6-31G* level of theory (Fig. 1). It is important to note that the *N*-1 anion is substantially lower in energy compared to the *N*-4 analog (Fig. 1). Predictably, the dipole moment of the anionic species is much higher than that of the neutral analog. However, it is interesting to note that the dipole moment corresponding to the *N*-4 anion is considerably higher compared to that of the *N*-1 anion. Thus, the microwave irradiation in general facilitates anion production and is more significant in the case of the less stable *N*-4 anion (see Table 2).

A quick look at Table 3 and Figure 1 indicates that the reaction profiles are virtually identical for all four substituents considered in this study.

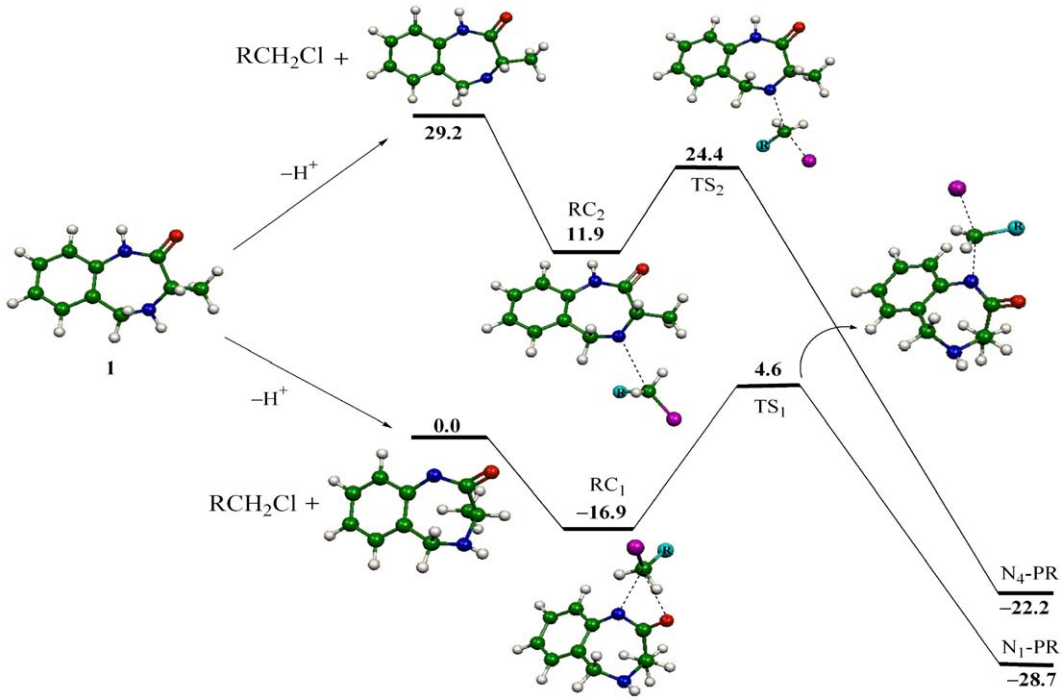


Figure 1. Reaction profile for both the products (*N*-1 and *N*-4) obtained at MP2/6-31G*//HF/6-31G*. Entry 1 of Table 1 is taken as the model alkyl group for the reaction profile.

Table 2. Calculated dipole moment for neutral (*N*-1H–*N*-4H), anions (*N*-1 and *N*-4), reaction complex (RC) and transition states (TS) at HF/6-31G* and MP2/6-31G*//HF/6-31G* in parentheses

Structure	Dipole moment (Debye)	
N-1H–*N*-4H	3.4 (2.8)	
N-1 anion	6.5 (5.6)	
N-4 anion	7.1 (6.6)	
	RC	TS
2a	2.1 (1.9)	8.4 (7.7)
2b	2.4 (2.7)	7.6 (6.8)
2c	3.2 (2.8)	8.0 (7.2)
2d	3.5 (3.6)	8.8 (7.9)
3a	4.1 (3.7)	8.5 (8.2)
3b	5.1 (4.8)	8.4 (8.0)
3c	4.6 (4.4)	7.6 (7.3)
3d	4.4 (4.2)	8.4 (8.0)

Table 3. Calculated central barriers and reaction energies (kcal/mol) for both (*N*-1 and *N*-4) products at HF (I) and MP2 (II) levels with the 6-31G* basis set

Structure	Central barrier		Reaction energy	
	I	II[a]	I	II[a]
2a	18.0	21.5	−33.3	−28.7
2b	17.3	20.8	−29.1	−25.8
2c	19.4	23.6	−31.7	−25.3
2d	16.8	19.8	−31.6	−25.4
3a	11.1	12.5	−55.4	−51.4
3b	12.1	13.3	−57.7	−53.2
3c	13.0	14.1	−57.0	−51.0
3d	11.7	13.7	−56.9	−50.9

[a] Single point calculation on HF/6-31G* optimized geometries.

It is noted that the more stable anion has a significantly high barrier for the consequent nucleophilic substitution, while the *N*-4 anions have a very small barrier for the generation of the product. Therefore, while the nucleophilic substitution is the rate-determining step for the formation of the *N*-1 PR, the formation of the *N*-4 anion is the rate-determining step for the formation of the *N*-4 PR. The thermal pathway adopts the lower energy profile resulting in the preferential production of the *N*-1 PR. However, the microwave irradiation facilitates anion production owing to a higher change in the dipole moment along the deprotonation pathway. Thus, the microwave radiation triggers abundant anion production with a slight preference for the *N*-4 anion, although it has higher energy. As the consequent step is very facile once the *N*-4 anion formation takes place, the regioselectivity is established. It is to be noted that the MW pathway has a much more negative free energy of reaction compared to the thermal reaction, thus the MW effects will be substantial in stabilizing that route.[1c,12] Therefore, these computational studies account for the observed switch over of the regioselectivity going from thermal to microwave irradiation.

In conclusion, we have described the regioselective aminoethylation of 1,4-benzodiazepin-2-one by changing the mode of the energy source to furnish either the *N*-1 or *N*-4 aminoethylated products. The regioselectivity in the aminoethylation was explained by considering the extent of the polarity of the transition state and on the basis of the rate-determining step involved under both conventional heating and microwave conditions. Calculations also suggested that the specific microwave effects can be explained by considering the dipole

moment differences from reactant to intermediate anions and transition states. Microwave irradiation facilitates the route B mechanism (Scheme 2) in which the difference in the dipole moment from **1** to the *N*-4 anion and its consequent transition state are relatively higher whereas under conventional conditions the reaction follows route A for the *N*-1 aminoethylation as nucleophilic substitution is the rate-determining step.

Selected spectral data—1-(2-Dimethylaminoethyl)-3-methyl-1,3,4,5-tetrahydrobenzo[e][1,4]diazepin-2-one (**2a**)

^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ 7.26–7.15 (m, 4H), 4.31–4.17 (m, 1H), 4.04 (d, 1H, $J = 11.6$), 3.66 (d, 1H, $J = 11.6$), 3.63–3.60 (m, 1H), 3.27 (q, 1H, $J = 6$), 2.73–2.41 (m, 2H), 2.13 (s, 6H), 1.87 (br s, 1H, NH), 1.15 (d, 3H, $J = 6.4$). MS (FAB): *m*/*z* (%) 248 (100) $[M+1]^+$, 204 (65) $[M-N(CH_3)_2]^+$.

4-(2-Diethylaminoethyl)-3-methyl-1,3,4,5-tetrahydrobenzo[e][1,4]diazepin-2-one (**3b**)

^{1}H NMR ($CDCl_3$, 200 MHz, TMS): δ 8.73 (br s, 1H, NH), 7.28–7.21 (m, 2H), 7.11 (d, 1H, $J = 8$), 7.03–6.99 (m, 1H), 3.99 (d, 1H, $J = 11.6$), 3.91 (d, 1H, $J = 11.6$), 3.54 (q, 1H, $J = 6$), 2.89–2.66 (m, 8H), 1.34 (d, 3H, $J = 6.8$) 1.12 (t, 6H, $J = 7.2$).

MS (FAB): *m*/*z* (%) 276 (100) $[M+1]^+$, 190 (25) $[M-CH_2N(CH_2)_2(CH_3)_2]^+$, 176 (20) $[M-CH_2CH_2-N(CH_2)_2-(CH_3)_2]^+$.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.03.094.

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11. (a) *Typical experimental procedure: Aminoethylation of 1,4-benzodiazepin-2-one under conventional heating conditions*: A mixture of 1,4-benzodiazepin-2-one **1** (400 mg, 2.27 mmol), alkyl halide hydrochloride (3.41 mmol), K_2CO_3 (942 mg, 6.82 mmol), and dry DMF (10 ml) was heated for 6–8 h at 80 °C. Work-up and column chromatography over silica gel furnished **2a**–**d**.; (b) *Aminoethylation of 1,4-benzodiazepin-2-one under microwave conditions*: Domestic microwave oven—power input: 230 V AC/50 Hz; Output: 900 W (IEC 705 rating standard); microwave frequency: 2450 MHz; power consumption, microwave 1350 W. As described above instead of heating for 6–8 h at 80 °C, the mixture was irradiated with microwaves for 90 s.
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