RSC Advances

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Capture of benzotriazole-based Mannich electrophiles by CH-acidic compounds†

Cite this: *RSC Advances*, 2013, **3**, 4152

Received 8th November 2012,
Accepted 14th January 2013

DOI: 10.1039/c3ra22826f

www.rsc.org/advances

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The Mannich-type capture reaction of aminoalkylbenzotriazoles by CH acidic compounds is documented. The pK_a of the benzotriazole counteranion is key to the success of such reactions, whereas the global electrophilicity of the reactive iminium moiety is secondary.

Developing facile methods for carbon–carbon bond formation continues to be a synthetic challenge, especially in the context of continuously expanding molecular diversity. Aminoalkylations are powerful synthetic tools since they combine the creation of a new carbon–carbon bond with an increase in molecular diversity and functionality by the introduction of an amino moiety. For instance, Patterson *et al.* recently reported an aminoalkylation reaction as a key step in the synthesis of 1-(1-(benzo[*b*]thiophen-2-yl)cyclohexyl)piperidine analogs as inhibitors of trypanothione reductase.[1] Over many decades, the Mannich reaction has been considered as the most important methodology for the aminoalkylation of C–H acidic compounds.

In the Mannich reaction, a C–H group is α-aminomethylated by an iminium compound, generally formed *in situ*.[2] Overall the acidic H of the C–H group is converted to CR^1R^2–NR^3R^4. Originally, R^1 and R^2 were both H, but the versatility of the reaction was broadened by the development of variants using preformed aldimines, iminium salts, aminals or hemiaminals as Mannich electrophiles. Recent developments in the field have renewed interest in the Mannich reaction, including intramolecular, organocatalytic,[3–6] catalytic[7] and stereoselective variants,[8–10] often supported by new technological breakthroughs.[11] Furthermore, the products of such reactions, the so-called Mannich bases, have found numerous applications as building blocks. Classically, the reaction requires harsh and prolonged conditions thus restricting its scope. A significant diversification is exemplified by the development of mild benzotriazole-mediated aminoalkylations and related reactions.[12–15] Benzotriazole-based aminoalkylating reagents have been readily utilized with various nucleophiles, including: enolates,[16] imidazolidine derivatives,[17] isonitriles,[18] enol ethers,[19–22] enamines,[20,22,23] and enamides.[22,23]

Many active pharmaceutical ingredients (APIs) are obtained through a key Mannich step or display the typical core of a Mannich base.[24,25] The most famous include tropanone and derivatives,[26] rifamycin,[27] tramadol,[28–30] procyclidine,[31–33] falicain,[34] fluoxetine,[35,36] rolitetracycline[37,38] and tolmetin.[39–41]

In this communication, we now report the reaction of various aminoalkylbenzotriazoles with a small library of C–H acidic compounds. The reactivity of aminoalkylbenzotriazoles (**1**) is rationalized by means of computational chemistry (global electronic properties and thermodynamic considerations).

We selected a small library of representative compounds **1a–i** (Fig. 1) from the range of aminoalkylbenzotriazoles reported in the literature.[12,42–44] The behavior of compounds **1a–i** has been studied in the past by spectroscopic and semi-empirical methods, in solution and in the solid state.[45–47] They have been shown to act as milder sources of electrophilic iminium cations **3a–e** than the corresponding Eschenmoser's salts **2a,b**.[16,48] It is well-known that aminoalkylbenzotriazoles equilibrate in solution to mixtures of N^1 and N^2 isomers, the reactivity of which towards nucleophilic displacement is similar,[45–47] in agreement with our computations.

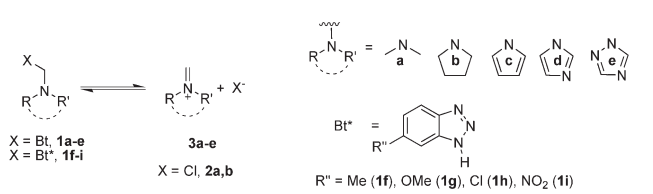

Fig. 1 Selection of Mannich electrophiles (see Tables 1 and 2 for Gibbs free energies and enthalpies of reaction).

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† Electronic supplementary information (ESI) available: Detailed computational procedures and thermochemical data. See DOI: 10.1039/c3ra22826f

Table 1 Chemical potential (μ), global hardness (η) and global electrophilicity (ω) for iminium species **3a–e**

Iminium	μ (u.a.)	η (u.a.)	ω (eV)
3a	−0.4108	0.2776	8.3
3b	−0.3862	0.2470	8.2
3c	−0.3733	0.1276	14.9
3d	−0.3996	0.1353	16.1
3e	−0.4303	0.1629	15.5

The values reported in Table 1 refer to the N^1 isomers. Data for the N^2 isomer can be found in the ESI.†

At first, we looked at global electrophilicity (ω) of the iminium species **3a–e** (see Table 1 and ESI† for detailed procedure), as we suspected that global electronic properties would be responsible for reactivity towards nucleophiles.[49–57] Results from Table 1 show that the iminium species **3a–e** are strong electrophiles on the electrophilicity scale[57] and this electrophilicity is enhanced in the aromatic pyrrolyl **3c**, imidazoyl **3d** and triazoyl **3e** iminium species.

The position of the equilibrium linking precursors **1a–e**, **2a,b** and the corresponding iminium species **3a–e** was computed at the B3LYP/6-31+G** level of theory in the gas phase at room temperature and in THF at room temperature and reflux (see computational details in ESI†). In total agreement with experimental observations, the equilibrium is predicted to be more towards the formation of the iminium species **3a,b** in the case of the Eschenmoser's salts than for their benzotriazole surrogates. The latter are thus latent sources of iminium cations. Table 2 indicates that, despite the very high electrophilicity of the corresponding iminium cations, the pyrrolyl (**1c**), imidazoyl (**1d**) and triazoyl (**1e**) compounds are significantly less prone to release their iminium counterpart than the dimethyl (**1a**) or pyrrolidine (**1b**) analogs.

To extend the scope of this preliminary study, we also considered the effect that various EWG (electron-withdrawing) and EDG (electron-donating) groups would have on the benzotriazole moiety modulating the reactivity of the corresponding aminoalkylbenzotriazoles **1f–i**, using 1-((pyrrolidin-1-yl)methyl)-1*H*-benzo[*d*][1,2,3]triazole **1b** for comparison (Table 3). Thermochemical computations revealed that strong electron withdrawing groups such as NO_2 allowed for similar ΔG° values as the chloro-analogs **2a,b** (see compound **1i** in Table 3).

Table 2 Reaction parameters for the formation of iminium species **3a–e** from **1a–e** and **2a,b**. Reaction parameters are given in kcal mol^{-1}

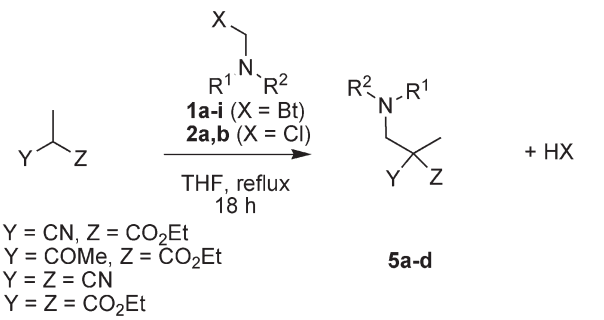
	Gas phase rt		THF rt		THF reflux	
Compound	ΔG°	ΔH°	ΔG°	ΔH°	ΔG°	ΔH°
1a	112.3	124.9	22.0	34.6	20.4	34.5
1b	107.6	119.8	19.9	32.3	18.3	32.2
1c	139.6	151.1	51.1	63.0	49.5	62.9
1d	152.8	164.3	61.8	74.1	60.2	74.1
1e	162.9	174.9	70.7	82.6	69.1	82.5
2a	110.9	119.1	9.2	16.0	8.3	15.9
2b	106.3	114.1	8.4	15.2	7.4	15.2

Table 3 Reaction parameters for the formation of iminium species **3b** from **1f–i**. Reaction parameters are given in kcal mol^{-1}. No significant differences in activity were computed between the 5- and the 6-substituted benzotriazoles (see ESI)

		Gas phase rt		THF rt		THF reflux	
Compound	EDG/EWG	ΔG°	ΔH°	ΔG°	ΔH°	ΔG°	ΔH°
1f	Me	108.8	120.9	21.1	33.3	19.4	33.3
1g	OMe	108.3	121.3	21.3	34.5	19.5	34.5
1h	Cl	101.9	114.1	17.3	29.7	15.6	29.6
1i	NO_2	102.2	113.3	20.6	31.9	10.2	24.1

Ethyl cyanopropanoate **4a** is commercially available and was selected as a model CH-acidic compound for a preliminary investigation. *N*-Aminoalkylbenzotriazoles **1a–i** and the related chloro-compounds **2a,b** were screened for Mannich-type capture reactions (see Scheme 1 and experimental details in the ESI†).

The best results were obtained for compound **1b**, with 61% conversion after 18 h under reflux in THF (Table 4). A lower conversion was observed for the reaction with **1a**. For the heteroaromatic series, 20% conversion was obtained for **1c** while reactions with **1d,e** failed. This trend in capture activity for compounds **1a–e** follows the variation in ΔG° disclosed in Table 2. Surprisingly, the capture reaction with the classical Mannich electrophiles **2a,b** failed, although the computed ΔG° indicated a favorable shift of the equilibrium towards the iminium species **3a,b**. Furthermore, modification of the benzotriazole moiety either



Scheme 1 Mannich type capture of CH-acidic compounds **4a–d** with *N*-aminoalkylbenzotriazoles **1a–i** and related chloro-compounds **2a,b**.

Table 4 Yield of the Mannich type capture of ethyl cyanopropanoate **4a** with *N*-aminoalkylbenzotriazoles **1a–i** and related chloro-compounds **2a,b**

Mannich electrophile	Yield (%)
1a	44
1b	61
1c	20
1d	0
1e	0
1f	39
1g	49
1h	54
1i	51
2a	0
2b	0

by including EDG or EWG substituents (compounds **1f–1i**) lowered the yield in comparison to the original compound **1b**. The latter results clearly indicate the impact of the pK_a of the counteranion generated (X) on the capture reaction: in the cases of **2a,b**, the counteranions generated are weak bases, unable to deprotonate **4a**, despite a favourable equilibrium towards **3a**. For compounds **1h,i**, the introduction of an EWG on the benzotriazole lowers ΔG° but also impacts on the pK_a of the corresponding benzotriazolate (pK_a = 8.56, 7.62 and 6.31 for X = H, Cl and NO_2, respectively).[58] The introduction of an EDG (compounds **1f,g**) slightly increases the pK_a of the corresponding benzotriazolate but also impacts on ΔG°, becoming less favorable for the iminium species **3b**. According to these results, **1b** was selected for further testing.

To obtain further evidence for the pK_a-sensitivity of the Mannich-type capture step, other commercially available CH acidic compounds were considered for reaction with **1b** including ethyl 2-methyl-3-oxobutanoate **4b** (pK_a = 12.3),[59] methyl malonitrile **4c** (pK_a = 12.4),[60] diethyl 2-methylmalonate **4d** (pK_a = 17)[58] and ethyl cyanopropanoate **4a** (pK_a = 9).[59] The following yields were obtained: 61, 29, 27 and 4% for the capture of **1b** by **4a–d**, respectively, showing clearly a linear correlation between the pK_a of the CH acidic compound and the yield of the reaction with **1b**.

Conclusions

This preliminary work documents the reactivity of aminoalkylbenzotriazoles as Mannich electrophiles. In their reaction with CH acidic compounds, several factors have been identified: (*i*) the reaction heat for the formation of the iminium cation, (*ii*) the pK_a of the counteranion X, and (*iii*) the pK_a of the CH acidic partner. The pK_a of both X and the CH acidic compound appears to be crucial, whereas global electrophilicity of the corresponding iminium cation seems to be secondary. These observations are consistent with thermodynamic control of the reaction.

Acknowledgements

This work was supported by the Research Foundation-Flanders (FWO-Vlaanderen; fellowship to JCMM). JCMM acknowledges the ICT Department of Ghent University for access to HPC facilities. The authors acknowledge the Kenan Foundation (University of Florida), the King Abdulaziz University (Saudi Arabia) and Henkel Ireland Ltd. for financial support and permission to publish. Dr N. Lefevre is acknowledged for stimulating discussions.

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