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Synthesis of 1-aryl-3*H*-[1,2,5]triazepino[5,4-*a*]benzimidazol-4(5*H*)-ones and quantum chemical investigation of the rotamers of the Boc-protected hydrazide key intermediate

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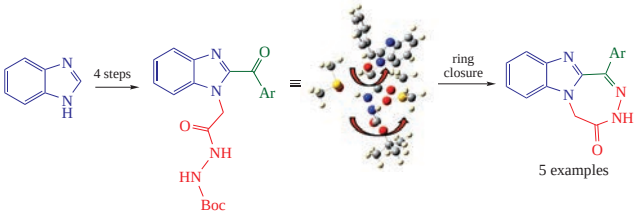
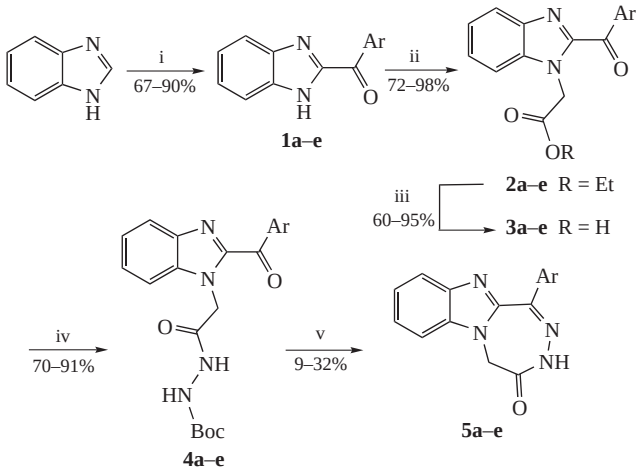
3*H*-[1,2,5]Triazepino[5,4-*a*]benzimidazol-4(5*H*)-ones were obtained in five steps involving C-acylation of benzimidazole, its N-alkylation with ethyl bromoacetate, the ester hydrolysis, condensation with BocNHNH$_2$, and the acid-catalyzed heterocyclization of thus obtained 2-(2-aroyl-1*H*-benzimidazol-1-yl)-*N*′-(*tert*-butoxycarbonyl)acetohydrazides. The geometry of *tert*-butyl carbazate rotamers was estimated with quantum chemical calculations.



Benzimidazole derivatives play a significant role in organic and medicinal chemistry.[1–7] In continuation of our effort to synthesize triazepine derivatives,[8–10] we report here the preparation of a novel ring system containing two important cores, namely, benzimidazole and triazepinone ones.

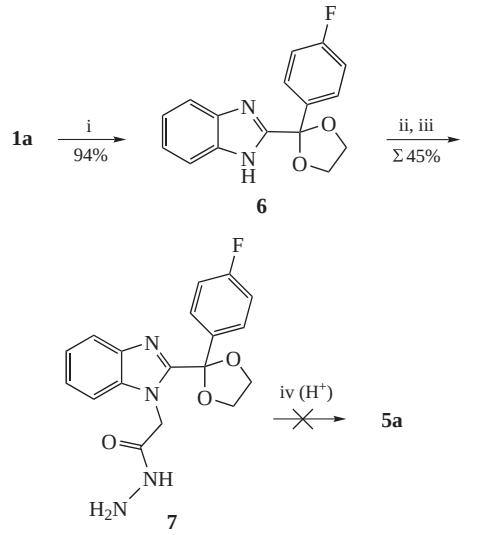
Initially, 2-aroylbenzimidazoles **1a–e** were prepared from benzimidazole and benzoyl chlorides under basic conditions according to the reported procedure[11] (Scheme 1). Compounds **1a–e** were alkylated with ethyl bromoacetate in the presence of Cs_2CO_3[12] to give intermediates **2a–e**. Mild hydrolysis of ethyl esters **2a–e** with 5% aqueous solution of NaOH and subsequent reaction of the carboxylic acids **3a–e** with *tert*-butyl carbazate (BocNHNH$_2$) in the presence of 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU) coupling reagent afforded hydrazides **4a–e** in good overall yields. Protected hydrazide **4b** (Ar = Ph) was treated with a catalytic amount of 10% aqueous solution of HCl in boiling ethanol according to our earlier procedure,[9] however, complete decomposition was observed and product **5b** was not detected by HPLC-MS. Unfortunately, similar results were obtained when sulfuric, *p*-toluenesulfonic and trifluoroacetic acids were tested as catalysts. Finally, when solutions of protected hydrazides **4** and pyridinium *p*-toluenesulfonate (PPTS) in ethanol were refluxed for 48 h, one-pot deprotection and ring closure reaction took place. The target compounds, 1-aryl-3*H*-[1,2,5]triazepino-[5,4-*a*]benzimidazol-4(5*H*)-ones **5** were obtained in low to moderate yields after chromatographic purifications.



Scheme 1 *Reagents and conditions*: i, ArCOCl, Py, Et_3N, room temperature, 3 h, then 40% NaOH, reflux, 1 h; ii, $BrCH_2CO_2Et$, Cs_2CO_3, $MeCN/CH_2Cl_2$, room temperature, ~18 h; iii, 5% NaOH, THF/EtOH, room temperature, 20 min, then 1 M HCl; iv, BocNHNH$_2$, HATU, DIPEA, THF, room temperature, 2 h; v, PPTS, EtOH, reflux, 48 h.

The synthesis of the desired 1-aryl-3*H*-[1,2,5]triazepino[5,4-*a*]-benzimidazol-4(5*H*)-ones **5** was also attempted in a different pathway (Scheme 2). This synthetic approach commenced with a *p*-toluenesulfonic acid catalyzed protection of the carbonyl group of 2-(4-fluorobenzoyl)-1*H*-benzimidazole **1a** with ethylene glycol[13] to give dioxolane **6**. The N-alkylation of intermediate **6** with ethyl 2-bromoacetate in the presence of Cs_2CO_3[12] led to the corresponding ethyl benzimidazole-1-acetate derivative whose hydrazinolysis afforded hydrazide **7**. Unfortunately, the anticipated cleavage of the dioxolane ring and the subsequent cyclization did not occur upon applying the usual acid-catalyzed methods[14] the starting compound **7** remained unchanged.

The structures of the new compounds were confirmed by IR, ^{1}H and ^{13}C NMR measurements as well as by HRMS. In the ^{1}H NMR spectrum (DMSO-d_6) of Boc-hydrazides **4**, the Boc methyl groups resonated as an interesting non-symmetric multiplet that was a result of a non-equivalence of protons due to retarded rotation. For all five hydrazides **4a–e** three rotamers could be detected in a ratio of 67:18:15 based on the ^{1}H NMR measurements. The structure of the possible conformational isomers was



Scheme 2 *Reagents and conditions*: i, $HOCH_2CH_2OH$, *p*-TsOH, 120 °C, 7 h; ii, $BrCH_2CO_2Et$, Cs_2CO_3, $MeCN/CH_2Cl_2$, room temperature, ~18 h; iii, $N_2H_4{\cdot}H_2O$, EtOH, reflux, 48 h; iv, H_3O^+ ($HCl/H_2O/EtOH$/reflux, or $HClO_4/CH_2Cl_2$/room temperature, or $H_2SO_4/H_2O/CH_2Cl_2/SiO_2$/room temperature, *cf*. ref. 14).

investigated in detail for compound **4b** with quantum chemical calculations. The geometry of the conformers was based on the assumed rotation around the two amide bonds, leading to four corresponding conformers (Figure 1). The geometries of the conformers were optimized, and the distribution of the conformers was determined (for details, see Online Supplementary Materials). The ωB97XD/6-311G++(2d,2p) method considering the implicit DMSO solvent model together with two explicit DMSO molecules gave the nearest distribution values compared to the experimental values (see Online Supplementary Materials, Table S2). When taking a closer look at the conformers, two times two pairs can be considered depending on the bonds rotated: **4′b**–**4′′′′b**, **4′′b**–**4′′′b**, or **4′b**–**4′′′b**, and **4′′b**–**4′′′′b**. Regarding the experimental results, three ^{1}H NMR peaks were observed for the Bu^t group in an intensity ratio of 67:18:15. The three peaks at 1.504, 1.335 and 1.253 ppm could be attributed to the 15, 67 and 18% conformers, respectively. We have assumed that the different chemical shifts of the Bu^t hydrogen atoms were influenced by the different electron withdrawing effect of the oxygen atom connected to the Bu^t group. Considering the atomic charge distributions in terms of Natural Population Analysis (NPA), one might see that the relative charge of the C(=O)–O–CMe_3 is changing in the order **4′′′b** (–0.586), **4′b** (–0.582), **4′′′′b** (–0.578), **4′′b** (–0.573). It shows that the relative charge of the oxygen atom is the least negative in rotamer **4′′b**, therefore it draws less electron density from the alkyl group thus causing the most upfiled chemical shift (calculated amount: 19%, measured: 18% at 1.253 ppm). On the contrary, conformer **4′′′b** (calculated: 11%) has the largest negative charge causing the most downfield chemical shift (measured: 15% at 1.504 ppm). It is assumed that the other two conformers (**4′b** and **4′′′′b**, calculated populations: 60 and 10%, respectively) having similar charges (–0.578 and –0.582, respectively) between those of **4′′b** and **4′′′b**, are detected as one peak at 1.335 ppm (measured: 67%).

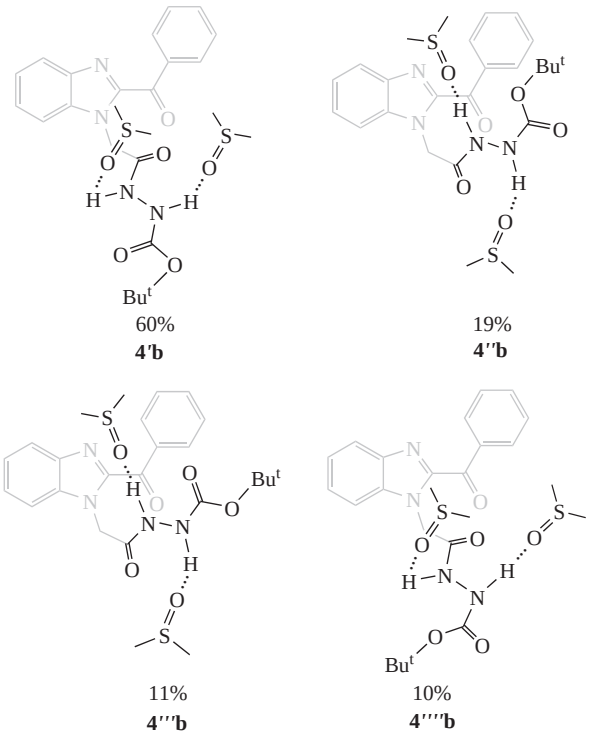


Figure 1 Structures and calculated populations of four possible conformers of compound **4b**.

In summary, five representatives of 1-aryl-3*H*-[1,2,5]triazepino-[5,4-*a*]benzimidazol-4(5*H*)-ones **5a**–**e** containing a novel benzene-fused triazepino imidazole ring system have been synthesized. The ^{1}H and ^{13}C NMR spectra of their precursors **4** showed distinct rotamers in DMSO-d_6. The conformers were examined with quantum chemical computations and the calculated distribution based on the conformational analyses and NBO population analysis corresponded to the experimentally observed ratio of the conformers, and moreover, the distribution of the chemical shifts was explained as well.

Online Supplementary Materials

Supplementary data associated with this article (experimental and computational details, NMR and IR spectra) can be found in the online version at doi: 10.1016/j.mencom.2019.05.017.

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