

Applications of caged-designed proton sponges in base-catalyzed transformations



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Dedicated to Professor Milan Kratochvíl for his 90th birthday anniversary.

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ABSTRACT

Superbasic properties of caged proton sponges (PSs) – substituted diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecanes (DTDs) – were utilized in Knoevenagel and Claisen–Schmidt condensations, the Pudovik reaction, and Michael addition. This investigation covers the influence of the solvent, reaction temperature, catalyst loadings as well as the electronic properties of substituents upon the reaction. Moreover, we provided an activity comparison between our new base and a well-known and commercially available proton sponge® (DMAN). The basicity (in MeCN) of our chosen DTD ($pK_{BH^+} = 21.7 \pm 0.1$) exceeded the prototypal PS – 1,8-bis(dimethylamino)naphthalene (DMAN, $pK_{BH^+} = 18.6$), by three orders of magnitude. We proved that DTDs are reasonably active species in monitored reactions, which is a consequence of a hydrogen bridge angle ($\approx 130^\circ$) between the two nitrogen atoms and the captured proton. We present here syntheses of aminoindolizine, substituted 4*H*-chromene, and flavanones, and the unexpected formation of a bis-addition product formed after Michael addition, all under mild conditions.

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1. Introduction

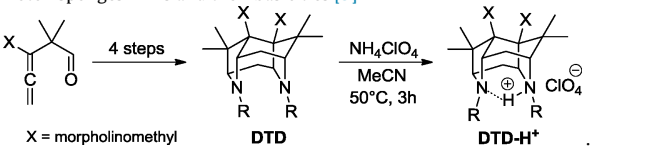
Building a carbon–carbon single bond is one of the most important procedures in synthetic chemistry and requires accurate information about the possibilities and conditions of such transformations. Most frequently, base catalysis serves as a tool for the production of both fine chemicals and intermediates. Hence, chemists from all research areas try to develop smart catalytic systems based on organic [1], organometallic [2], or inorganic [3] structures, sometimes fixed at various carriers [4]. It is not surprising that many of them are “green” and recyclable and that the development of such chemicals is an area of growing interest. Solid bases are preferred over liquids because of their economic and environmental impacts connected with the recoveries of catalysts. All these requirements are fulfilled by our newly developed generation of PSs – diazatetracyclo[4.4.0.1^{3,10}.1^{5,8}]dodecanes (DTDs) [5]. They exhibited very good activity when tested and measured at classical condensation reactions, as shown in our study. At the same time, their resistance to highly basic and acidic conditions as well

as toward nucleophiles was observed. Neither their decomposition nor transformation were observed even after one week. It is actually disputable whether we should call them directly proton sponges or proton-sponge-like compounds. Nevertheless, their physicochemical properties are in good agreement with established knowledge. In general, PSs are organic diamines with unusually high basicity where the two basic nitrogen centers are in close proximity to each other. This orientation allows the uptake of one proton to yield a structure stabilized by an intramolecular hydrogen bond [6]. The first of them, DMAN, was reported by Alder in 1968 [7]. This compound has a basicity about 10 million times higher than other similar organic amines. Two general protocols have been established to raise the thermodynamic basicity or proton affinity. In one, the naphthalene skeleton is replaced by another aromatic spacer, thus influencing the basicity by varying the nonbonding N–N distance. The second approach focuses on the substitution at the nitrogen atoms or their adjacent environment (buttressing effect) [8]. In this way, several different structures with superbasic properties can be prepared [9]. In our previous study, we contributed to this area with a new class of PSs having a rare rigid skeleton [5]. Their preparation was optimized and we are able to prepare them in 25–30% overall yields in an eight-step synthesis. We can change their pK_{BH^+} values by more than three orders of magnitude using different *p*-substituted benzyl bromides (Table 1).

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Table 1
Proton sponges DTDs and their basicities [5]



DTD/DTD-H ⁺	R	p <i>K</i> _{BH⁺} (DTD-H ⁺) (CD ₃ CN)
a	Me	22.6 ± 0.1
b	allyl	22.4 ± 0.1
c	benzyl	21.7 ± 0.1
d	<i>p</i> -NO ₂ -benzyl	19.0 ± 0.1
e	<i>p</i> -CN-benzyl	19.4 ± 0.1
f	<i>p</i> -CF ₃ -benzyl	20.0 ± 0.1
g	<i>p</i> -F-benzyl	21.1 ± 0.1
h	<i>p</i> -Me-benzyl	22.1 ± 0.1
i	<i>p</i> - <i>t</i> Bu-benzyl	22.0 ± 0.1
j	<i>p</i> -MeO-benzyl	22.2 ± 0.1
k	<i>p</i> -MeS-benzyl	21.6 ± 0.1

2. Experimental

2.1. General information

All reagents were purchased from commercial suppliers and redistilled or recrystallized. Solvents were dried and distilled by standard procedures and stored over molecular sieves (3 or 4 Å). All reactions were carried out under a dry argon atmosphere and followed by TLC (Merck F254 silica gel). Respective model reactions were monitored by dynamic proton NMR measurements (Bruker Avance 500).

2.2. Knoevenagel condensation: final procedure

Ethyl cyanoacetate – ECA (4 mmol, 426 μL) was mixed with propan-2-ol (2 mL) and aldehyde (8 mmol). Then, the catalyst was added (0.5 mol%, 12 mg of DTD or 4.3 mg of DMAN, respectively) and the reaction mixture was stirred at 50 °C under an argon atmosphere. The conversion was followed by proton NMR. After solvent removal, the residue was washed with Et₂O and the liquid part separated from the insoluble part. The solution consisted of Knoevenagel product and used aldehyde, which were separated by column chromatography. The solid part was the DTD catalyst and its regeneration involved washing with 5 M aqueous KOH and extraction with DCM. This procedure was carried out especially when larger scale reactions were performed, and by this simple method the catalyst was regenerated, usually with 90–95% effectiveness.

2.3. Claisen–Schmidt condensation: general procedure

Substituted benzaldehydes (2 mmol) and 2'-hydroxyacetophenone (2.1 mmol, 253 μL) were mixed together and the catalyst was added (2 mol%, 25 mg). The reaction mixture was stirred at 150 °C for 3 h under an argon atmosphere. The reaction was followed by proton NMR. After the consumption of aldehyde, the condensed intermediate 2'-hydroxychalcone (at lower temperature) or final flavanone were purified by column chromatography.

2.4. Pudovik reaction: general procedure

Diethyl phosphite (1 mmol, 129 μL) in solvent (4 mL) was mixed with aldehyde (1 mmol) and the catalyst (2 mol% = 12 mg, 4 mol% = 24 mg) and stirred at 50 °C. After completion, the solvent was evaporated and the crude mixture separated by column chromatography. In the case of rearrangement to phosphate, mobile

phase Et₂O/DCM = 1:5 effectively enabled separation of the formed products.

2.5. Michael addition: general procedure

Methyl acrylate (4 mmol, 360 μL) was added to a mixture of *i*PrOH (2 mL) and ECA (2 mmol, 213 μL). Then, the catalyst was added (1 mol%, 12 mg) and the reaction mixture was stirred at 50 °C for 2 h. Subsequently, the solvent was evaporated and the remainder was dissolved in Et₂O and filtered through a short column of silica gel. After solvent evaporation, we obtained a pure oily product in an almost quantitative yield (98%). This reaction works also under solvent-free conditions.

3. Results and discussion

In a previous paper [5], we demonstrated considerable structural relaxation upon the monoprotonation of DTDs by measuring bond angles and nonbonding N–N distances in the free base and its acid (Figs. 1 and 2). Clearly, the shape of the molecule is

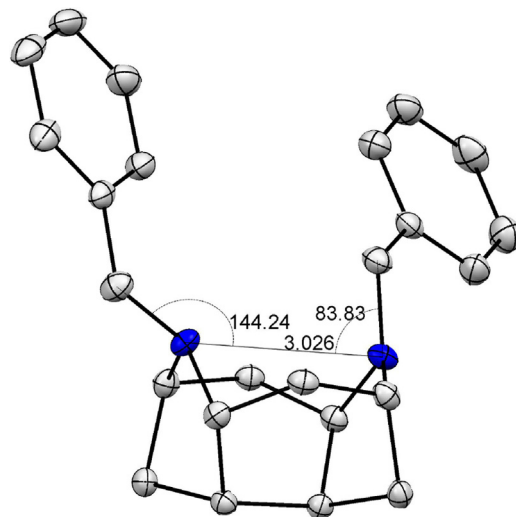


Fig. 1. ORTEP representation of DTD shown at the 50% probability level (upside-down view; hydrogen atoms and methyl and morpholinomethyl groups are omitted for clarity).

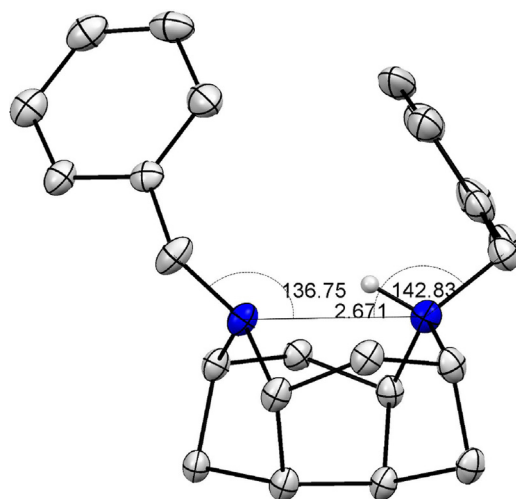


Fig. 2. ORTEP representation of DTD-H⁺ shown at the 30% probability level (upside-down view; hydrogen atoms (except for the captured proton), plus chloride anion, methyl and piperidinomethyl groups are omitted for clarity).

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