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Applications of Caged-Designed Proton Sponges in Base-Catalyzed Transformations

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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 ± 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 (≈130°) 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.

Key Words: proton sponge; base catalyst; Knoevenagel, Claisen-Schmidt and Pudovik ractions; Michael addition.

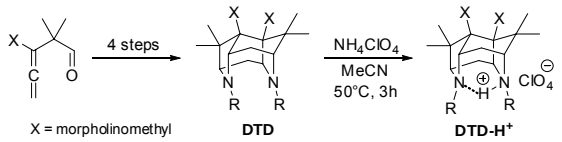
1. Introduction

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).

Table 1. Proton sponges DTDs and their basicities [5]



X = morpholinomethyl DTD DTD-H$^+$

DTD / **DTD-H$^+$**	R	pK_{BH}+ (**DTD-H$^+$**) (CD_3CN)
a	Me	22.6 ± 0.1
b	allyl	22.4 ± 0.1
c	benzyl	21.7 ± 0.1
d	*p*-NO_2-benzyl	19.0 ± 0.1
e	*p*-CN-benzyl	19.4 ± 0.1
f	*p*-CF_3-benzyl	20.0 ± 0.1
g	*p*-F-benzyl	21.1 ± 0.1
h	*p*-Me-benzyl	22.1 ± 0.1
i	*p*-*t*Bu-benzyl	22.0 ± 0.1
j	*p*-MeO-benzyl	22.2 ± 0.1
k	*p*-MeS-benzyl	21.6 ± 0.1

2. Experimental

2.1. General Information

All reagents were purchased from commercial suppliers and redistilled or recrystalyzed. 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 Et_2O 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 5M 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 hours 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 Et_2O / 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 hours. Subsequently, the solvent was evaporated and the remainder was

dissolved in Et_2O 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 (Figure 1 and 2). Clearly, the shape of the molecule is significantly changed by the action of the free electron pairs. The high basicity of such a rigid structure is caused by the release of energy after molecule protonation.

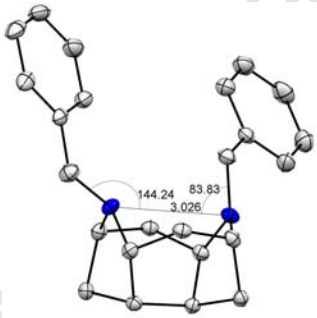


Figure 1. ORTEP representation of DTD shown at the 50% probability level (upside-down view; hydrogen atoms and methyl and morpholinomethyl groups are omitted for clarity).

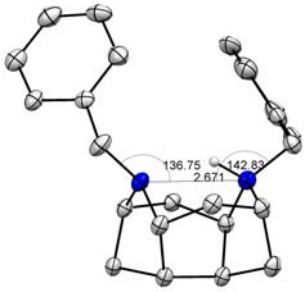
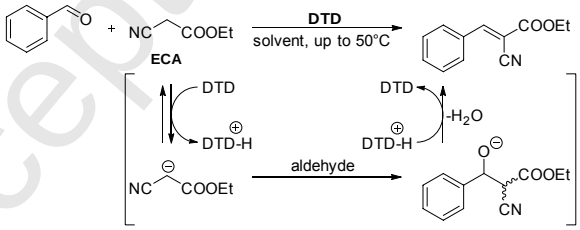


Figure 2. ORTEP representation of DTD-H$^+$ shown at the 30% probability level (upside-down view; hydrogen atoms (except for the captured proton), plus chloride anion, methyl and piperidinomethyl groups are omitted for clarity).

For our study, we selected DTDs with R = benzyl and X = piperidinomethyl groups (Table 1). Piperidinomethyl group was chosen instead of morpholinomethyl substitution because of its better solubility. Moreover, as expected, measurements showed the same basicities (21.7 ± 0.1) for both derivatives. We performed several types of base-catalyzed reactions to find suitable application for these promising molecules. As Knoevenagel condensation is a classical base-catalyzed reaction, we initiated our investigation in this area and started with the condensation of benzaldehyde and ethyl cyanoacetate (pK_a = 8.6) (Scheme 1). In all cases, optimized reaction conditions afforded the desired α,β-unsaturated product as *E*-isomer only. During the NMR measurements, we clearly recognized the presence of four possible diastereoisomers as intermediates, which provided the final condensed product after a water molecule elimination.



Scheme 1. Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate using the DTD catalyst.

A similar study with DMAN has already been published [10] and even the heterogeneous catalysis of immobilized DMAN on inorganic carriers appeared in literature [11]. We have conducted numerous experiments with ECA to set up the catalytic limits of DTDs. This means the determination of the most suitable solvent as well as the reactant molar ratios, the

catalyst loading, the reaction temperature, and even the concentration of the reaction mixture. We followed the change in conversion over time by proton NMR at appropriate intervals. First of all, we carried out several dynamic proton NMR measurements at different temperatures with a 1 : 1 molar ratio of reactants using 2 mol% of catalyst relative to aldehyde. The first experiments in $CDCl_3$ and CD_3CN showed very low conversions (Figure 3; the lowest two curves, experiments at 50°C). However, CD_3OD appeared to be a much more suitable environment (Figure 3; the three upper curves at three different temperatures). It was evident that the ion pair formed after the deprotonation step must be highly stabilized by solvation to be able to react with the submitted aldehyde. Otherwise, it would be immediately reprotonated as shown in Scheme 1. Thus, methanol with hydrogen bond donating and accepting abilities is a much more obvious choice, where the nucleophile formed *in situ* from ECA is a longer living system which subsequently attacks the carbonyl group. On the other hand, DTD-H^+ is deprotonated and refreshed *via* a hydrogen bond chain formed by the solvent.

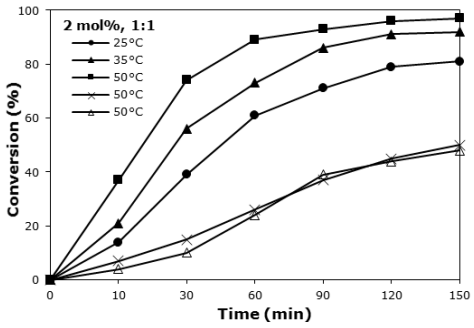


Figure 3. Dynamic proton NMR measurements of DTD catalytic activity in the benzaldehyde / ethyl cyanoacetate reaction in CD_3OD (the three upper curves) and in $CDCl_3$ vs. CD_3CN (the lowest two curves).

At this point, we were interested in reactions carried out with conventional heating and stirring. This change was immediately reflected in conversions and results obtained by NMR

tube experiments. We were able to reduce the reaction time and even the catalyst loading, the latter four times (0.5 mol%). Aliquots (100 μL) were taken from the reaction mixture at 30-minute intervals and analyzed by proton NMR. To fix the conversion, we quenched the reaction with trifluoroacetic acid (5 μL). We observed the considerable influence of the molar ratio of aldehyde / ECA upon the reaction (Figure 4). After 30 minutes in the presence of 1 mol% of catalyst at 50°C in MeOH, the aldehyde was fully consumed when the concentration of ECA was two times higher (1 : 2). The same conditions but without a solvent afforded the same results. However, solvent-free conditions could be used with liquid aldehydes only. This led us to apply an aldehyde / ECA molar ratio of 1 : 2 in the following reactions and even reduce the catalyst loading. It is worth noting that we used 2 mL of solvent in each reaction and that this amount appeared to be suitable on the milligram to four-gram scale.

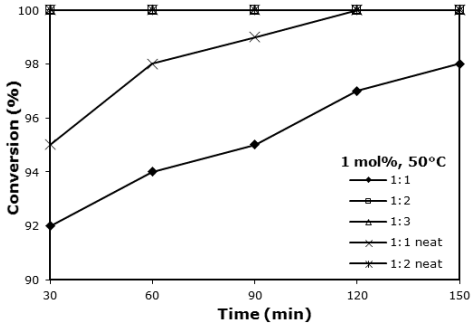


Figure 4. Effect of benzaldehyde / ethyl cyanoacetate molar ratio on reaction conversions in MeOH and under solvent-free conditions.

Then, we focused more deeply on the question of the used solvent and found that isopropanol was even better solvent for such a reaction, increasing the conversions to 96 % after 30 min with just **0.5 mol%** of catalyst at 50°C with a 1 : 2 molar ratio of reactants (Figure 5). We followed the influence of various solvents and found that ethyl acetate also worked fairly well. The reaction without any solvent, on the other hand, afforded the worst results. As mentioned above, previous results were fully confirmed here, and 1,2-dichloroethane (DCE)

and acetonitrile were shown to be the least efficient solvents. We observed just 60 % of conversion in MeCN after 30 minutes. We chose DCE instead of $CHCl_3$ because of its higher boiling point and lower reactivity at higher temperatures.

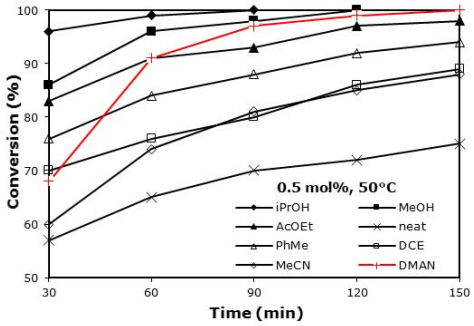


Figure 5. Effect of solvent on reaction conversion using DTD base and its comparison to the activity of DMAN catalyst in *i*PrOH.

Finally, we applied the known proton sponge® (1,8-bis(dimethylamino)naphthalene - DMAN) at most suitable reaction conditions (50°C, 0.5 mol%, *i*PrOH, ECA/aldehyde 1 : 2 ratio). From the beginning it is already clear, that DTD starts the catalyzed reaction very rapidly and the curve profile is almost flat. However, DMAN works much slower and the initial conversion (30 min.) is even lower than that for DTD in DCE (Figure 5). But after 60 minutes it reached the conversion in AcOEt environment and after 1.5 hours the conversion was already 95 %. These results show the difference in basicities between DMAN and DTD and, more importantly, they indicate a significantly higher kinetic activity in *i*PrOH for our base. However, DMAN's better solubility was reflected in the results under solvent-free conditions where even a 1:1 molar ratio of reactants worked well and considerably better than DTD (Figure 6). The curve profile almost duplicates the process taking place with DTD in *i*PrOH with a 1:1 ratio of reactants. In fact, these conditions are for DMAN even better than that used before. So we can conclude here that DTD works better in solution but DMAN, regarding its perfect solubility, works much better under solvent-free protocol.

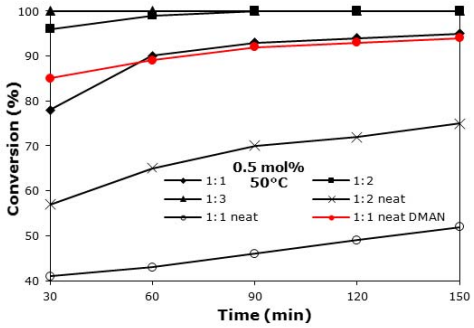


Figure 6. The results of reactions in *i*PrOH or at solvent-free conditions with 0.5 mol% of DTD and a solvent-free reaction using 0.5 mol% of DMAN catalyst and a 1:1 molar ratio of reactants.

Figure 6 further shows the results of reactions performed in *i*PrOH and without a solvent. From this graph, the importance of the solvent and the excess of ECA are evident. We also observed a rapid decrease in conversion compared to experiments with the 1 mol% of catalyst used before. After 120 min, we observed just 70% of the desired product against the full consumption of aldehyde in Figure 4. Then, we took inspiration from green chemistry principles and carried out the reaction under room temperature conditions (Figure 7). The result was surprising, because even 0.5 mol% of DTD afforded 91% conversion (after 2.5 h) and prolongation (≈ 6 h) led to completion of the reaction. Again, we performed the same reaction with DMAN and it was in a good agreement with our previous findings where DTD is much faster in the beginning but with time the process became almost equally efficient. But we must take into account the solubility factors for DTD at room temperature as well. Hypothetically, solvents like DMF, DMA, DMSO etc. would be just perfect but we wanted to show how the catalyst works in easily evaporable solvents and 50°C as working temperature using benign isopropanol are usable conditions for numerous reactions.

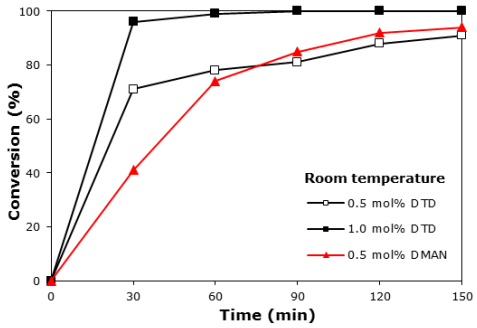


Figure 7. Reactions performed at room temperature in *i*PrOH.

We then considered whether our catalyst would work in very small amounts. Thus, we performed the reaction with 0.1 mol% of DTD at 80°C in *i*PrOH (2 mL). This means that for 4 grams of Knoevenagel product we used only 12 mg of DTD; the reaction was completed after 180 min. The scope of the method was further tested with several aromatic, aliphatic, and heteroaromatic aldehydes. We found that reaction times for their full consumption varied according to their aldehydic character (Figure 8).

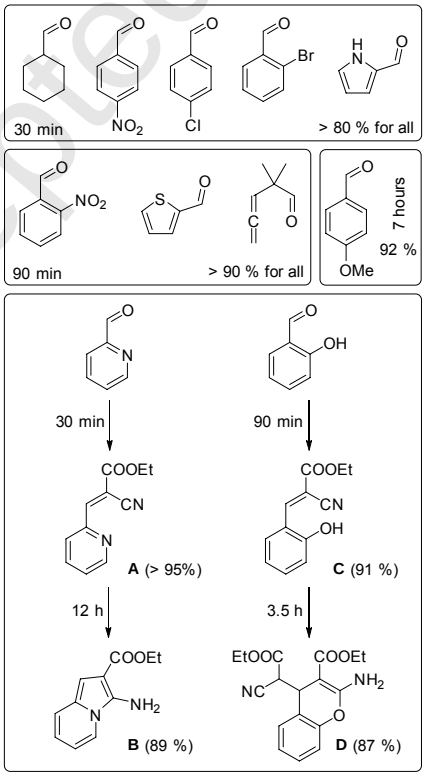


Figure 8. Condensation reactions of various aldehydes with ECA in *i*PrOH and their reaction times for full conversions with isolated yields including two cyclization reactions leading to heterocyclic products B and D.

Moreover, after an intramolecular cyclization of the Knoevenagel products **A** and **C,** 2-pyridinecarboxaldehyde and salicylaldehyde afforded aminoindolizine **B** [12] and 2-amino-4*H*-chromene **D** [13] in quantitative yields. Product **D** was formed as two diastereoisomers (ratio 1 : 2), i.e. we used either a 1 : 1 or 1 : 2 molar ratio of reactants. This means that molecule **C** reacted immediately with the presented ECA to the final compound **D** and that the second half of the starting aldehyde remained unconsumed in the reaction mixture. Further our attention was devoted to the least acidic activated methylene compound, ethyl malonate with pK_a = 13.3. This significantly less acidic starting material caused much more difficult deprotonation. Therefore we utilized 5 mol% of catalyst with longer reaction times. All the other reaction conditions as solvent, temperature and molar ratio of reactants stayed the same. Moreover, we tested the electronic influence of *p*-substitution on benzaldehydes upon the reaction (Figure 9). As expected, the best results afforded the condensation of *p*-nitrobenzaldehyde but the conversion has never exceeded 90 % even after 24 hours at 80 °C.

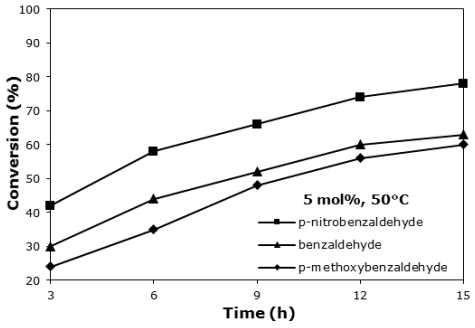
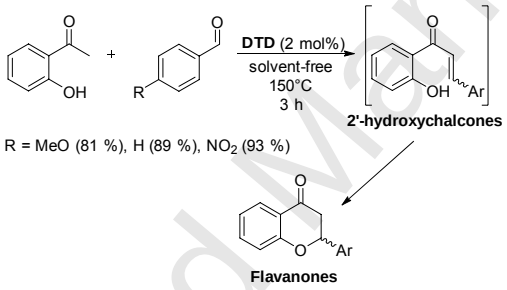


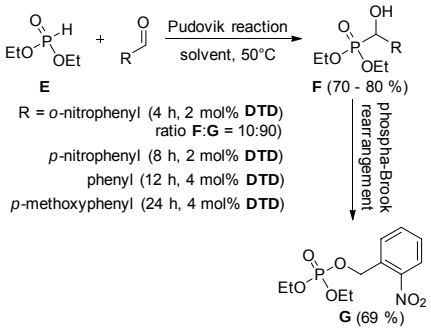
Figure 9. The results of condensations of benzaldehydes with ethyl malonate in *i*PrOH.

In order to investigate the scope of our DTD application as a base for further catalyzed reactions we tried the Claisen-Schmidt condensation reaction [14]. The first experiments in various solvents were not very successful and produced only negligible conversions to the desired flavanones (Scheme 2). Later, we performed this reaction at 150°C in a solvent-free arrangement, which turned out to be an ideal protocol. It highly accelerated the second step – intramolecular Michael addition at 2'-hydroxychalcones as intermediates. After chromatographic purification, three different benzaldehydes afforded very good to excellent yields. Under milder conditions (lower temperature and shorter reaction time) it was also possible to isolate chalcones, some of them known as biologically active species [15].



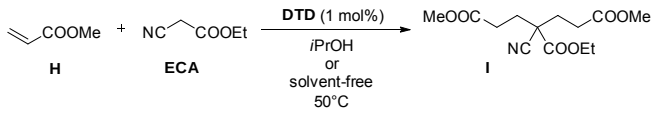
Scheme 2. Claisen-Schmidt Condensation with Isolated Yields.

We also tested our catalyst DTD in the Pudovik reaction [16], which is a straightforward powerful method for creating a single C-P bond. It is a reaction involving dialkyl phosphites (in our case, diethyl phosphite **E**), which are deprotonated in a basic environment and, after addition to the submitted aldehyde, afford α-hydroxyphosphonates **F** (Scheme 3). There is also an enantioselective version of this reaction [17]. An important aspect here is the possible rearrangement of the formed phosphonates **F** to phosphates **G**. In the Brook rearrangement, an organosilyl group R changes position with the proton of an hydroxy group, all under the influence of a base. The reaction product is then a silyl ether [18]. The authors call it a phospha-Brook rearrangement, and it proceeds when an electron withdrawing group is bound in α-position to carbonyl functionality [19].



Scheme 3. Pudovik reaction and subsequent phospha-Brook rearrangement with isolated yields.

The first step, the Pudovik reaction itself, proceeds fairly well in different types of solvents, starting from polar aprotic (DCM, DMF, MeCN) to polar protic ones (EtOH, iPrOH). However, ethanol appeared to be the most suitable one. In the case of this solvent, after 2 hours at 50°C with 2 mol% DTD, we observed the formation of products **F** and **G** in the ratio 20 : 80 %. Prolongation of the reaction to 4 hours led to 90 % of **G**; however, we never observed full conversion to phosphate **G**, even after 24 hours. In acetonitrile, the situation after 2 hours was exactly the opposite (**F** : **G** = 80 : 20 %). We tested four benzaldehydes (Scheme 3) and the results confirmed that without an electron withdrawing group at the α-position no rearrangement proceeds. Moreover, even *p*-nitrobenzaldehyde showed a twice longer reaction time. Thus, it was not surprising that benzaldehyde and its *p*-methoxy analog reacted very slowly. However, with one more equivalent of DTD (4 mol%) both reactions were completed after 12 and 24 hours, respectively.



Scheme 4. Michael addition of ethyl cyanoacetate and methyl acrylate in quantitative yield.

The last base-catalyzed reaction investigated in our study was Michael addition, which is one of the most often used and elegant ways of forming a C-C single bond. We used ethyl cyanoacetate as a Michael donor, and methyl acrylate **H** as a Michael acceptor (Scheme 4). We obtained the same results both in the presence of a solvent and without it. The formed molecule was not the expected product of the simple addition of a nucleophile prepared *in situ* on α,β-unsaturated ester **H.** Instead, triester **I** formed from 1 molecule of ECA and two molecules of ester **H** was identified [20]. In the case of the reactants having a molar ratio of 1 : 1, one half of ECA was still unconsumed. Enlargement of the molar ratio in favour of acrylate (1 : 2) led exclusively to unexpected product **I** of very high purity.

4. Conclusions

Superbasic properties of caged proton sponges (PSs) – substituted diazatetracyclo[4.4.0.$1^{3,10}$.$1^{5,8}$]dodecanes (DTDs) – were demonstrated in several base-catalyzed transformations in the role of base. Knoevenagel and Claisen-Schmidt condensations, the Pudovik reaction, and Michael addition were carried out to investigate their activity. During the test, the influence of the solvent, reaction temperature, catalyst loading, and substituents upon the reaction was followed. It was shown that the catalyst was active in the range of 0.1 – 5mol%. Moreover, a catalytic activity of commercially available DMAN proton sponge® was compared to DTD in Knoevenagel condensation reaction. We observed a considerable influence of solvent upon the reaction, where DTD was more active in solution and, on the other hand, DMAN under a solvent-free arrangement. This was explained by the significant differences in catalysts solubilities.

Acknowledgements

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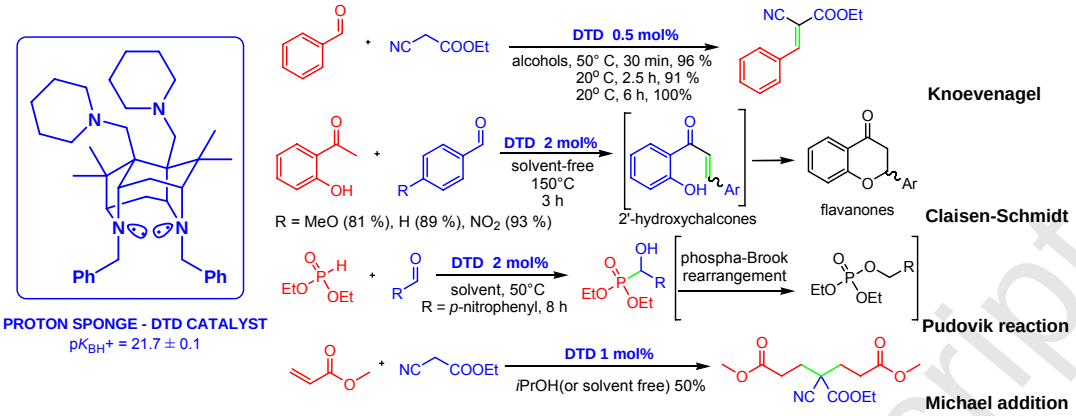

Graphical abstract

Highlights

- Superbasic properties of a new proton sponge were tested in base catalysed reactions.
- Activity comparison between new base and proton sponge® (DMAN) was performed.
- The new catalyst was very active in solvents, DMAN in solvent free conditions.