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A one-pot synthesis and self-assembled superstructure of organic salts of a 1,5-benzodiazepine derivative

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Abstract—A one-pot reaction of *o*-phenylenediamines with acetone in the presence of catalytic amounts of different organic acids under solvent-free conditions afforded 1,5-benzodiazepine derivatives in excellent yields at room temperature. The supramolecular organization of the co-crystals of the benzodiazepine with trimesic acid and picric acid shows ladder and brick wall superstructures via the formation of conventional and nonconventional hydrogen bonding networks.

Benzodiazepines are interesting compounds because they belong to an important class of the pharmacologically pre-eminent 1,5-benzodiazepines which have been extensively used as anticonvulsant, antianxiety, analgesic, sedative, antidepressive and hypnotic, and antiinflamatory agents.[1–4] In particular, 1,5-benzodiazepines are useful precursors for the synthesis of fused ring benzodiazepine derivatives,[5,6] such as triazolo, oxadiazolo, oxazino, and furano benzodiazepines. Due to their wide range of applications,[7] these compounds have received a great deal of attention in connection with their synthesis. Many reagents have been reported in the literature for the condensation of *o*-phenylenediamines with acetone, including BF_3–etherate, polyphosphoric acid, $Yb(OTf)_3$ and $MgO/POCl_3$, sulfated zirconia, and ionic liquid medium.[8–10] The difficulties encountered in the cyclization of these seven-membered heterocycles limited their structural studies. In recent years, organic reactions on solid phase have received considerable interest in organic synthesis because of their ease of handling, enhanced reaction rates, greater selectivity, and simple work-up.

Nature relies on the power of self-assembly to construct complex supramolecular architectures.[11] Intermolecular interactions play a central role in supramolecular chemistry, materials science, and biology through self-assembly processes. The amazing supramolecular constructs are collections of molecular building blocks organized with remarkable precision by a multitude of weak, but cooperative, noncovalent bonds. Self-assembly of specific solid structures continues to be a theme of current interest for developing materials with enhanced optical, electrical, or catalytic properties.[12] Although it is still difficult to predict how a particular molecule will pack in the solid state, considerable progress has been achieved in recent years in this respect.[13,14] There is a significant amount of interest in the use of salts in the pharmaceutical industry because certain properties of the solid forms can be modified without altering the desired effect of the drug. Each salt imparts unique properties to the parent compound. The selection of the best salt form for an ionizable drug is now of paramount importance in the pharmaceutical development of new chemical entities.[15]

Herein, we report the efficient one-pot synthesis of a 1,5-benzodiazepine in good yield at room temperature. We also report on the structural study of the supramolecular self-assembly of the organic salt of the 1,5-benzodiazepine with trimesic acid and picric acid. The self-assembled organic network shows ladder and brick wall superstructures, respectively, via the formation of conventional and nonconventional hydrogen bonds.

As a part of our studies to explore the utility of simple solid phase room temperature grinding methods in solvent-free conditions, we decided to investigate the use of an organic acid, as a catalyst for the preparation of 2,3-dihydro-2,2,4-trimethyl-1*H*-1,5-benzodiazepine by

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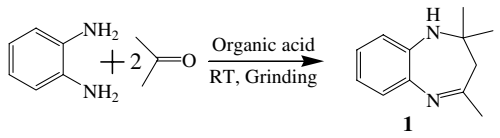


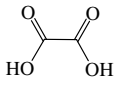
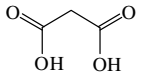
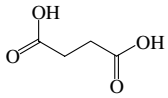
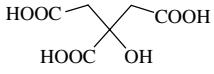
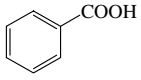
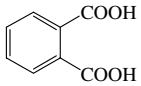
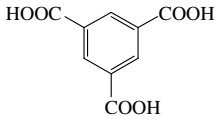
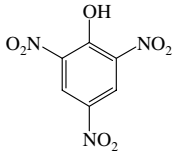
Scheme 1. Synthesis of compound **1**.

condensation of acetone with *o*-phenylenediamine (Scheme 1).

The reaction was carried out at room temperature using acetone and *o*-phenylenediamine in the presence of a catalytic amount of an organic acid.[16] The results are summarized in Table 1. Both aliphatic and aromatic acids containing mono-, di- or tri-carboxylic acid groups can act as the catalyst. The best results were obtained using 1,3,5-benzene tri-carboxylic acid (trimesic acid) as catalyst. In general, more acidic catalysts are more efficient for this procedure. The progress of the reaction was monitored by TLC; NMR and GC–MS were used for analysis of the products.

Compound **1**, when mixed with an equivalent amount of organic acid, forms a colorless salt with trimesic acid **1a** and a dark red salt with picric acid **1b** from water ethanol mixture at room temperature. The structures of the organic salts **1a** and **1b** were investigated by single crystal X-ray diffraction.[17] In the solid-state, the seven-membered heterocyclic ring adopts an armchair conformation. The imino nitrogen in **1** bears a small negative charge because of the resonance structure.[18] Hence it can accept one proton in the presence of an acid, which is reflected in the solid state structure. In the salt crystal, the C=N IR stretching frequency is lowered by ~40 cm^{-1} to 1600 cm^{-1} after protonation of pure **1**.

Table 1. One-pot synthesis of 1,5-benzodiazepine

Entry	Acid catalyst	Time	Yield[a] (%)
1		30 min	80
2		5 h	54
3		7 h	45
4		1 h	72
5		5 h	45
6		1 h	85
7		10 min	97
8		15 min	94

[a] Yields of the isolated product.

As shown in Figure 1, the crystal structure of **1a** consists of two crystallographically independent molecules of the heterocyclic ring in the asymmetric unit. The trimesic acid unit in **1a** forms a 2D tape along the *a*-axis via formation of strong O–H···O type hydrogen bonds (H···O = 1.75 Å).

The distances between the two 2D tapes are ~8.0 Å (Fig. 2). Two adjacent tapes are clipped together by heterocyclic rings through the formation of strong conventional N–H···O (average H···O = 1.98 Å) and weak nonconventional C–H···O (average H···O = 2.82 Å) and C–H···π (average H···π = 3.43 Å) type hydrogen bonding. The heterocyclic rings are held together by weak C–H···π (average H···π = 3.18 Å) bonding. However, the three-dimensional arrangement of the molecules in the crystal lattice is unique and quite

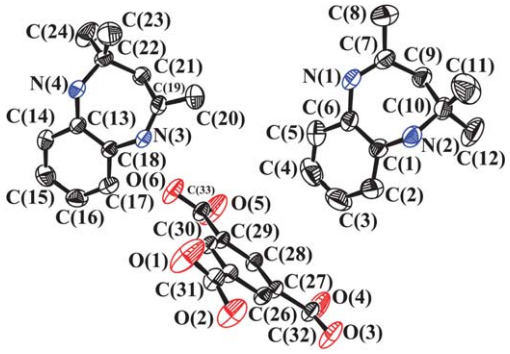


Figure 1. ORTEP plot of **1a**.

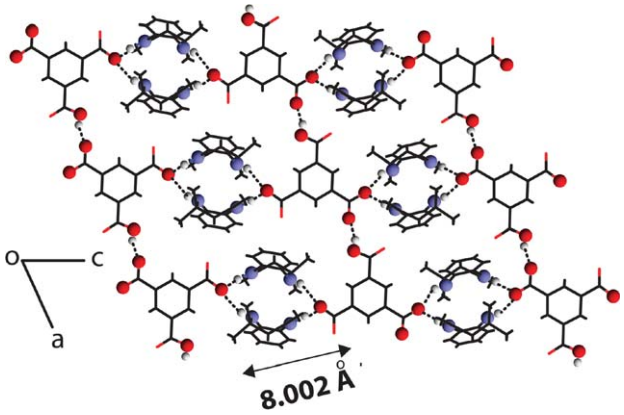


Figure 2. O–H···O and N–H···O type H-bonding in **1a**.

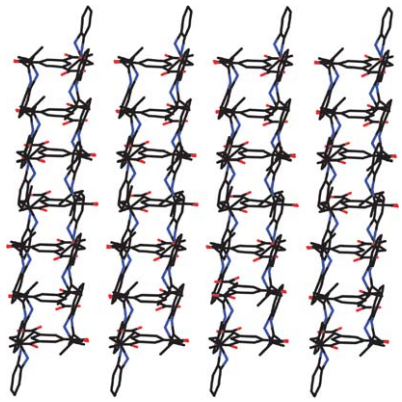


Figure 3. 3D ladder framework of **1a** along the *c*-axis.

fascinating. The packing analysis reveals that the two crystallographically independent heterocyclic rings are packed in an alternate layer in the crystal lattice in such a fashion that results in the formation of a 3D ladder-like framework (Fig. 3).

In salt, **1b** (Fig. 4) the picrates are held together by strong π···π interactions (3.37 Å) unlike in salt **1a**, where no such interactions are observed between the trimesic acid unit. The heterocyclic rings of **1b** are held together by strong N–H···N (H···N = 2.60 Å) type hydrogen bonding. Organic salt **1b** does not show any C–H···π type interactions like **1a**. Picrates form strong N–H···O (average H···O = 2.16 Å) and C–H···O (average H···O = 2.67 Å) type hydrogen bonding with neighboring heterocyclic rings which results in the formation of a 3D brick wall network along the *a*-axis (Fig. 5).

We have developed a simple, convenient and one-pot method for the synthesis of a 2,3-dihydro-1,5-benzodiazepines by the condensation of acetone with *o*-phenylenediamine using an organic acid as the catalyst under solvent-free conditions at rt. The present methodology offers very attractive features such as reduced reaction times and higher yields, which offer wide scope in organic synthesis. The operational simplicity of the procedure is also attractive. We have also shown that this pharmacologically important compound can be crystallized as an organic salt forming a self-assembled superstructure.

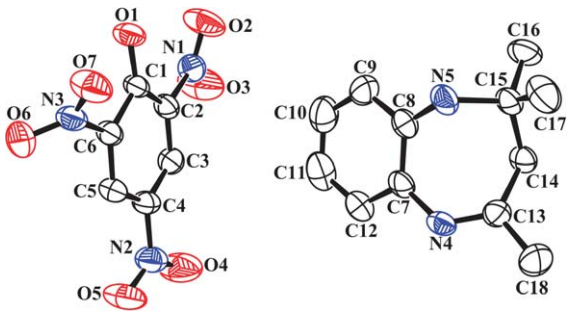


Figure 4. ORTEP plot of **1b**.

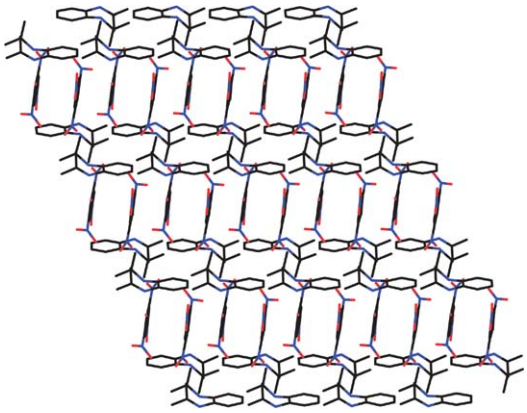


Figure 5. 3D brick wall framework of **1b** along the *a*-axis.

Acknowledgements

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16. *General procedure for the synthesis of 2,3-dihydro-1,5-benzodiazepines*: A mixture of organic acid (catalytic amount, 5 mol %) and *o*-phenylenediamine (5 mmol, 0.540 g) was thoroughly ground with a pestle in an open mortar at room temperature. The mixture was ground for 5 min until the mixture turned into a melt. Then, 10 mmol of acetone was added and grinding continued for the respective time mentioned in Table 1. The melt was then washed several times with cold alkaline water (pH $\sim$ 8.0). A yellow solid was obtained; mp 137–139 °C; GC–MS: $M^{+} = 188$. Anal. Calcd $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.37; H, 8.55; N, 14.83. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS) δ (ppm): 1.35 (s, 6H, 2 CH_3), 2.25 (s, 2H, CH_2), 2.35 (s, 3H, CH_3), 3.45 (br s, 1H, NH), 6.60–7.25 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ (ppm) 29.7, 30.4, 44.9, 68.3, 121.6, 122.0, 125.4, 126.7, 137.8, 140.6, 172.3. IR (KBr): ν/cm^{-1} 3290 (NH), 1638 (C=N), 1597 (Ar).
17. Crystal data for **1a**: CCDC # 290946; $C_{33}H_{38}N_4O_6$, M = 586.67, mp 185–187 °C, triclinic, *P*-1, $a = 9.4629(12)$ Å, $b = 9.5416(12)$ Å, $c = 19.182(3)$ Å, $\alpha = 83.930(3)°$, $\beta = 75.874(3)°$, $\gamma = 67.833(2)°$, $V = 1555.3(4)$ Å^3, $Z = 4$, $D_c = 1.359$ g cm^{-3}, $\mu = 0.107$ cm^{-1}, Mo-Kα radiation, $R1 = 0.0487$, $wR2 = 0.1329$, $S = 1.286$. Crystal data for **1b**: CCDC # 290945; $C_{18}H_{19}N_5O_7$, M = 417.38, mp 163–165 °C, triclinic, *P*-1, $a = 9.168(3)$ Å, $b = 9.417(3)$ Å, $c = 11.548(4)$ Å, $\alpha = 90.244(9)°$, $\beta = 103.886(8)°$, $\gamma = 97.315(9)°$, $V = 959.4(6)$ Å^3, $Z = 2$, $D_c = 1.167$ g cm^{-3}, $\gamma = 0.098$ cm^{-1}, Mo-Kα radiation, $R1 = 0.0981$, $wR2 = 0.2826$, $S = 2.009$. The crystallographic data for the complexes has been deposited with the Cambridge Crystallographic Data Centre. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam. ac.uk).
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