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COMMUNICATION

Pressure-accelerated copper-free cycloaddition of azide and alkyne groups pre-organized in the crystalline state at room temperature†

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We have designed a supramolecular system to pre-organize the azide and alkyne functional groups *via* electrostatic and arene–perfluoroarene interactions. After pre-organization, high pressure was applied to accelerate the copper-free cycloaddition of the azide and alkyne groups in the crystalline state.

Recently, pressure-accelerated/induced reactions have been gradually applied in syntheses, especially in organic syntheses in the solid state.[1] Advantages of such reactions include high yields, convenient work up and the "green" process. In these reactions, the cell volume shrinks under pressure, which leads to a decrease of the activation energy and acceleration of the reaction rate.[1e] Moreover, products of pressure-accelerated/induced reactions may be different to products resulting from thermal activation.[1b] This phenomenon has been found in various reactions, *e.g.*, [4 + 2] Diels–Alder cycloadditions,[2] List–Barbas–Mannich reactions,[3] and polymerizations.[1a]

The copper-catalyzed azide–alkyne cycloaddition (CuAAC) reaction has become the most important reaction in click chemistry due to its mild reaction conditions, high yields and regioselectivity.[4] To avoid the toxicity of the copper ions, great effort has been made towards developing copper-free AACs.[5] Many findings are striking in terms of further advancing the application of CuAAC click chemistry under aqueous condition.[6] Herein, we report an environmentally friendly and efficient pressure-accelerated copper-free AAC at room temperature. In this system, the azide and alkyne functionality were pre-organized in the crystalline state *via* electrostatic and arene–perfluoroarene interactions before high pressure was applied to accelerate the cycloaddition reaction to regioselectively afford 1,4-disubstituted triazole. The high pressure equipment used in this research was a hydraulic press and evacuable pellet die which were usually used to prepare standard IR samples. It actually produces over 1 GPa of pressure and is available for reactions up to the gram level. Moreover, a hydraulic press is more convenient and easier to handle, compared to expensive diamond anvil cells (DACs).

Electrostatic interaction is an important non-covalent interaction in supramolecular chemistry.[7–10] Recently, arene–perfluoroarene interaction has been gradually utilized in crystal engineering. Its binding energy is 3.7–4.7 kcal mol^{-1} in crystalline state,[11,12] which induces the alternating face-to-face stacking of phenyl and perfluorophenyl units.[13–16] Here we took advantage of these two non-covalent interactions to construct a supramolecular system in solid state with 4-ethynylaniline (**1**) and 4-azido-2,3,5,6-tetrafluorobenzoic acid (**2**). As shown in Fig. 1, electrostatic interactions link the amine and carboxylic acid in the horizontal direction, while arene–perfluoroarene interactions induced the face-to-face stacking in the vertical direction. The alkyne and azide functional groups were arranged in a favourable position for 1,3-dipolar cycloaddition which was then accelerated by pressure to afford a regioselective product in high yield.

1 and **2** were dissolved in common organic solvents, such as THF, acetone and methanol. Then solvents were removed under vacuum at room temperature to obtain the corresponding salt **1·2** as a yellow solid. The ^{1}H NMR spectra in $CDCl_3$ indicated that no reaction occurred during this process (see Fig. S7 in ESI†). In the powder X-ray diffraction (PXRD) pattern (Fig. 2a), the complex **1·2** showed completely different diffraction patterns in comparison to that from the simple mixing of **1** and **2**, suggesting that complex **1·2** was a co-crystal or an assembly of **1** and **2**. Fig. 2b shows the IR spectra of **1**, **2** and complex **1·2**. In the case of **2**, the 1709 cm^{-1} peak could be assigned to the

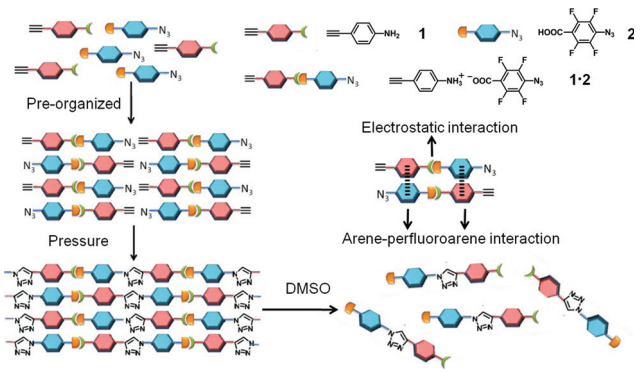

Fig. 1 Schematic representation of the pressure-accelerated 1,3-dipolar cycloaddition of the azide and alkyne groups pre-organized *via* electrostatic and arene–perfluoroarene interactions.

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†Electronic supplementary information (ESI) available: Experimental details, ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra, single crystal data and structure refinement of complexes **1′·2** and **2·3**. CCDC reference numbers 874309 and 874310. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2gc36069a

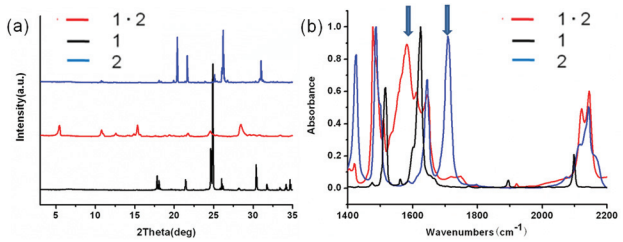

Fig. 2 (a) Powder X-ray diffraction: red, black, and blue lines correspond to complex **1·2**, **1** and **2**, respectively. (b) FT-IR in the solid state: red, black, and blue lines correspond to complex **1·2**, **1** and **2**, respectively.

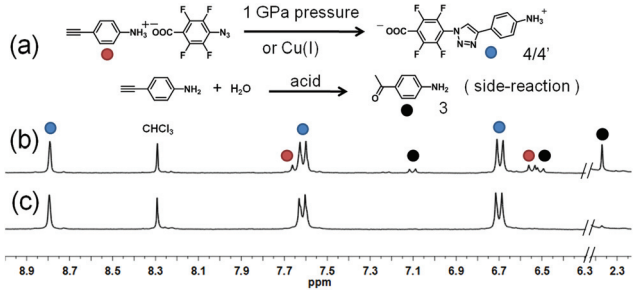

Fig. 3 (a) Reaction conditions. 1,3-dipolar cycloaddition: r.t., 1 GPa, overnight or r.t., CuI, THF, Et_3N. Hydration: air, 24 h. Partial ^1H NMR spectra of product in DMSO-d_6 (b) crude (c) after wash with $CHCl_3$ and acetone.

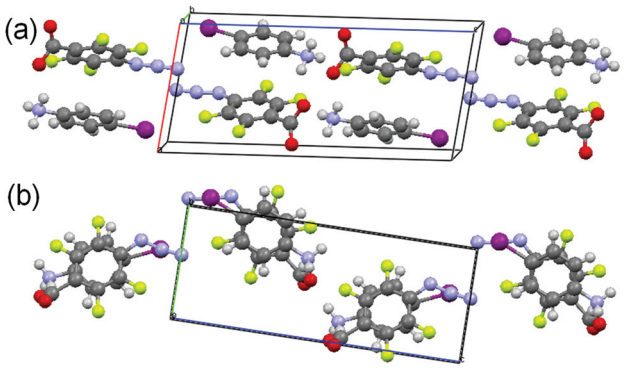

Fig. 4 ORTEP drawing of the crystal structure of **1′·2** with 30% probability thermal ellipsoids along [100] (a) and [010] (b).

C═O group. In salt **1·2**, that peak shifted to 1582 cm^{-1}, which indicated the deprotonation of the carboxylic acid to the carboxylate anion.[10] We considered that the carboxylate group and the ammonium group were strongly associated with electrostatic interactions.

As a control molecule, 4-azidobenzoic acid (**2′**) was also studied. In the IR spectra of a mixture of **1** and **2′**, prepared by the same method of salt **1·2** (see Fig. S10 in ESI†), the wavenumber shift of the C═O group was not observed, indicating no salt formation between **1** and **2′**, as the acidity of **2′** is not strong enough. In the PXRD experiment (see Fig. S11 in ESI†), the diffraction patterns of the **1** and **2′** mixture were only the simple addition of the patterns of the two individual compounds. Both results demonstrated that fluorination was essential for the formation of the salt **1·2**.

It was found that because of the electron-donating effect of amino group, **1** could be easily transformed into ketone **3** through a hydration reaction when catalysed with acid, such as hydrochloric acid, trifluoroacetic acid, perfluorobenzoic acid and **2**. In solution, the hydration process took several hours at room temperature. In the solid state it took about 24 hours to complete the hydration under normal humidity. However, in the anhydrous environment, hydration was suppressed and the yellow complex **1·2** gradually transformed into a pale white solid under normal pressure in 1 month, which was no longer soluble in THF, acetone and methanol, but soluble in DMSO. Raman and ^1H NMR spectra indicated that the main product was the cycloaddition product **4**.

Because of the side reaction, heating was not suitable to accelerate the cycloaddition of the azide and alkyne groups in this system. We chose to use high pressure to accelerate the reaction, taking advantage of the pre-organization of the functional groups, also avoiding the moisture. A hydraulic press and evacuable pellet die were used to produce the high pressure. Under 1 GPa pressure (Fig. 3), such a cycloaddition reaction was accelerated and completed overnight with an 80–90% yield, as indicated by ^1H NMR. Only a small amount of hydration by-product **3** was observed. To certify the regioselectivity, a copper catalyzed 1,3-dipolar cycloaddition of **1** and **2** was carried out to yield compound **4′** which was the same as **4**, confirmed by ^1H NMR and MS. Under the assumption that the CuAAC product is 1,4-disubstituted triazole, **4** should also be 1,4-disubstituted and the pressure-accelerated cycloaddition is regioselective. Similar to our previous study,[5k] we proposed that in the crystalline state the azide and alkyne groups were in an arrangement that is close to the transition state of the 1,4-disubstituted cycloaddition. High pressure was applied to accelerate the reaction by bring the functional groups closer.

To further elucidate the pre-organization of the azide and alkyne groups in the crystals, we attempted to grow crystals of complex **1·2**, but only obtained the co-crystal of **2** and **3** due to the hydration reaction during the crystal growing process. Therefore, as a model to evidence the arene–perfluoroarene and electrostatic interactions, crystals of **1′·2** was successfully obtained.‡ Compound **1′** (4-iodoaniline) is the precursor of **1** and has a similar size and electronic effect compared with **1**. Single crystal X-ray analysis (Fig. 4) revealed a columnar packing of the salt **1′·2** in the crystal. This columnar network structure is mainly composed of the carboxylate oxygen atoms of the carboxylic acid anions and the ammonium hydrogen atoms of the protonated amine. The phenylene and tetrafluorophenylene stack alternately in a face-to-face fashion and the distance between the two parallel aromatic rings is *ca.* 3.5 Å. The shortest distance between an iodine atom and an azide nitrogen atom within a column is 3.6 Å. To validate such a comparison between **1·2** and **1′·2**, we studied the PXRD of these two complexes. As shown in Fig. S14, S16 and Table S1 (see ESI†), the PXRD of **1·2** and **1′·2** were very similar. Furthermore, the simulated crystal structure of **1·2** was obtained from **1′·2** by replacing the iodine atom with the alkyne group using Materials Studio.[17] It was found that the simulated diffraction patterns of the crystal of **1·2** fits the

experimental XRD result very well, which indicated that the crystal structures of **1·2** and **1′·2** should be very similar. Therefore, we reasonably assume that in the crystal of **1·2**, both of the arene–perfluoroarene interactions and electrostatic interactions contribute significantly and the azide and alkyne groups are positioned suitably for the regioselective cycloaddition.[5k]

In summary, we have designed a supramolecular system to pre-organize azide and alkyne functional groups in the crystalline state *via* electrostatic and arene–perfluoroarene interactions. After pre-organization, high pressure was applied to accelerate the cycloaddition of the azide and alkyne groups with reaction times shortened from 1 month to 12 hours. A hydraulic press was used as the high pressure equipment in AACs for the first time. The orientation of the reacting functional groups might be suitable to generate 1,4-disubstituted triazoles and therefore promote a relatively well-controlled regioselective cycloaddition. This is a good example of a pressure-accelerated reaction with high regioselectivity, resulting from suitable packing through two non-covalent interactions cooperatively, which also provides a new direction to make chemistry "green" by using supramolecular chemistry.

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Notes and references

‡Crystal data for **1′·2**: $C_{13}H_7F_4IN_4O_2$, M = 454.13, monoclinic, space group, $P2_1$, a = 7.2406(14) Å, b = 6.3111(11) Å, c = 16.211(3) Å, β = 98.719(7)°, V = 732.2(2) Å^3, T = 173 K, Z = 2, m = 2.249 mm^{-1}, D_c = 2.060 g cm^{-3}, $F(000)$ = 436, λ = 0.71073 Å, total of 5741 reflections collected, 3087 independent reflections (R_{int} = 0.0264), R_1 [$I > 2\sigma(I)$] = 0.0261, wR_2 [$I > 2\sigma(I)$] = 0.0618, R_1 [all data] = 0.0265, wR_2 [all data] = 0.0621. CCDC 874309.† Crystal data for **2·3**: $C_{15}H_{10}F_4N_4O_3$, M = 370.27, triclinic, space group, $P\bar{1}$, a = 5.7206(11) Å, b = 10.897(2) Å, c = 12.306(3) Å, α = 86.60(3)°, β = 84.86(3)°, γ = 80.87(3)°, V = 753.5(3) Å^3, T = 173 K, Z = 2, m = 0.149 mm^{-1}, D_c = 1.632 g cm^{-3}, $F(000)$ = 376, λ = 0.71073 Å, total of 6742 reflections collected, 3423 independent reflections (R_{int} = 0.0400), R_1 [$I > 2\sigma(I)$] = 0.0532, wR_2 [$I > 2\sigma(I)$] = 0.1303, R_1 [all data] = 0.0604, wR_2 [all data] = 0.1360. CCDC 874310.†

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