Synlett M. Kazem-Rostami Letter

Facile Preparation of Λ-Shaped Building Blocks: Hünlich Base Derivatization

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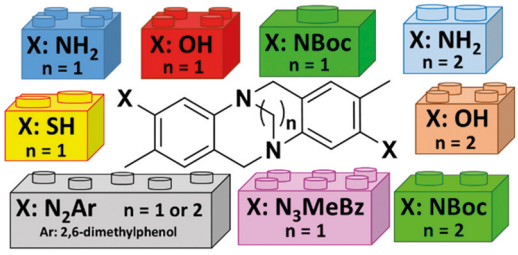

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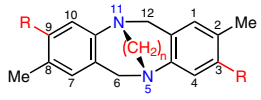
Abstract Hünlich's base modification has resulted in introducing a series of versatile Λ-shaped building blocks presented in this work. The methods are optimized to provide convenient approaches in the quicker production of these new building blocks in low-cost and low-risk.

Key words amines, bicyclic compounds, azo compounds, diazo compounds, nucleophilic aromatic substitution, phenols, protecting groups, thiols

Tröger's base analogues (TBAs) are tetracyclic boomerang-shaped molecules whose aromatic moieties nearly stand in a perpendicular dihedral angle to one another. The bent-shaped chiral core of TBAs is generated by two tertiary amine groups which flank a diazocine strap. Depending on which side of the molecule the strap is located, the handedness of TBAs is determined as an *SS* or *RR* enantiomer. Various TBAs structures have been elucidated by single-crystal X-ray crystallography.[1,2]

TBAs have played a substantial role as versatile building blocks employed in the design of Λ-shaped photoswitchable molecular hinges,[3,4] chiral ligands,[5] catalysts,[6] receptors,[7–9] supermolecules,[10] sensors,[7,11] polymers,[12] molecular tweezers, and leashes.[13] Although numerous methods have reported the production of TBAs including azide or triazole carrying ones;[2,14] up to the date, no TBA has been produced carrying triazene or sulfhydryl functional groups which would be useful in coordination,[15] polymer,[16,17] surface,[18] and organometallic/heterocyclic[19] chemistries. Triazene group can be converted into functionalized lactams,[20] triazoles,[21] dibenzopyranones, and coumarins, [22] or be utilized as a substrate for perfluoroalkylation reactions.[23] Furthermore, the triazene group can be replaced with many other functional groups[24,25] by being consumed as a diazonium source in organic solutions[25] or ionic liquids.[26] For instance; herein, a bistriazene TBA **1** (Table 1) is produced and converted into its corresponding bisthiophenol derivative **2** to introduce the first TBA-possessing sulfhydryl groups. This conversion achieved under a method reported in 2012.[25] This work not only introduces the first sulfhydryl and triazene carrying TBAs but also elaborates a quicker and much safer method of the preparation of bishydroxyl- and ethano-strapped TBAs using inexpensive materials.

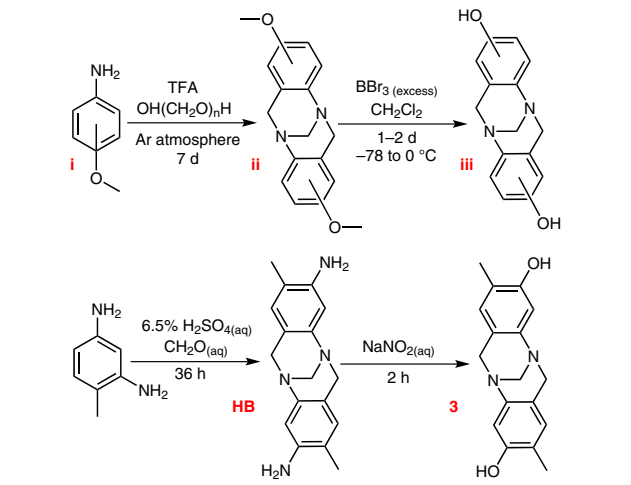
Table 1 Synthesis of the Building Blocks



Entry	Compd[a]	Time (h)	R Substituent;[b] [n]	Yield (%)
1	**1**	3.5	3-benzyl-3-methyl-1-triazene; [1][35]	60
2	**2**	2.5	SH; [1][36]	19
3	**3**	2.5	OH; [1][37]	96
4	**4**	6	*tert*-butyl carbamate; [1]	92
5	**5**	12	*tert*-butyl carbamate; [2]	77
6	**6**	9	4-hydroxy-3,5-dimethylphenyl diazene; [1]	83
7	**7**	12	4-butoxy-3,5-dimethylphenyl diazene; [1]	71
8	**8**	8	4-hydroxy-3,5-dimethylphenyl diazene; [2]	78
9	**9**	24	4-butoxy-3,5-dimethylphenyl diazene; [2]	22
10	**10**	1	NH_2; [2]	96
11	**11**	2.5	OH; [2]	91
12	**12**	18	OH; [0]	trace
13	**13**	2.5	H; [1]; 1,7: OH; and 4,10: Me	92

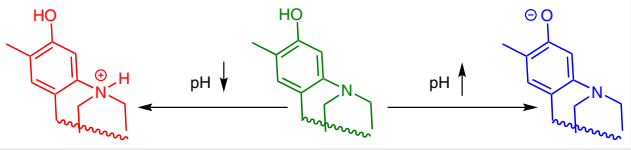
[a] Compound (racemate).
[b] R is symmetrically positioned on 3 and 9 positions.

The preparation of dihydroxy TBAs (Scheme 1, **iii**) has been performed by using the excess amounts of extremely hazardous and expensive reagents such as boron tribromide and trifluoroacetic acid (TFA).[9,27]



Scheme 1 The previously reported method on the preparation of dihydroxy TBAs (top) and the inexpensive shortcut introduced in this work (bottom).

The production of **iii** is time-consuming and requires several days to complete the trogeration (Scheme1, the conversion of **i** into **ii**) and the demethylation steps (the conversion of **ii** into **iii**).[27] Furthermore, due to the low solubility of the produced dihydroxy TBA **iii** in organic solvents, the separation of the product is problematic. In fact, every slight increase or decrease of pH value can easily transform the product into phenoxy form or quaternary amine salt, respectively (Scheme 2); which both tend to remain in the aqueous layer and hence the extraction becomes troublesome.[27] To display the pH-sensitive features of such molecules, the UV-vis spectra of **3** was obtained in the presence of strong protonating and deprotonating reagents (p. 46, Supporting Information). Compound **3** experienced a tremendous bathochromic shift upon deprotonation and turned red in color; however, the protonation led to a normal hypsochromic shift.



Scheme 2 The pH-sensitive nature of typical dihydroxy TBAs, e.g. **3**

The attempts on demethylation of **ii** under harsh and acidic conditions, HCl–AcOH (1:1, 110 °C, 48 h) instead of using BBr_3, only gave a mixture of **iii** and its asymmetrically methylated derivative which carries a hydroxyl group as well as an intact methoxy.[9]

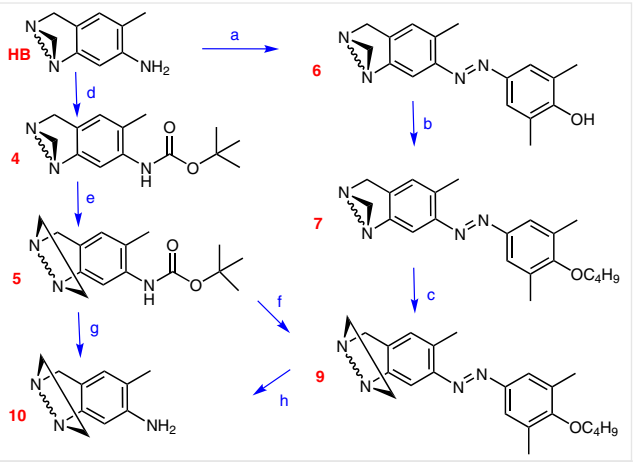
The literature also introduces the preparation of dihydroxy TBAs by the reduction of benzyl ether carrying analogues in the presence of hydrogen gas, and Pd/C catalyst.[27] This method is as costly as the aforementioned ones, in addition, requires the stream of an explosive gas or specialized hydrogenation reactor(s) which are only applicable in small batches. Although BBr_3 has apparently[9,27,28] covered the tedious production of hydroxyl-carrying TBAs, the involved risks and costs cannot be ignored and yet an alternative method is needed to be found. Therefore, an easier method (Scheme 1, bottom) on the production of dihydroxy TBAs (Table 1, compounds **3**, **11**, and **13**) is described in this work. Hünlich's base (Scheme 1, HB) is an affordable diamino TBA that facilitates the synthesis in the big scale in much lower costs. Furthermore, additionally introduced methyl groups significantly increase the hydrophobicity of **3**, **11**, and **13** products which helps their extraction during the workup.

The applied method in the production of **3**, **11**, and **13** is known as the decomposition of diazonium salts in aqueous media[16] which is optimized here to result in the facile production of the dihydroxy TBAs. This method[16] uses a diluted aqueous solution of sulfuric acid (H_2SO_4/H_2O, v/v 6.5%) instead of an expensive and fuming acid (neat TFA), and a harmless sodium nitrite solution ($NaNO_2$ in H_2O, w/v 3%) instead of boron tribromide which is violently corrosive, expensive, problematic to store and handle. Delightfully, the production of **3**, **11**, and **13** included none of the aforementioned drawbacks and resulted in the excellent amount of yields (91–96%).

TBAs structure has been modified by replacing the diazocine strap as well as changing the substituents.[29,30] Such structural modifications result in the emergence of enhanced properties. For instance, replacing the methylene group of the diazocine bridge by an ethylene group simply prevents the racemization[4] of TBAs in acidic media. Furthermore, such a modification gives new features to these valuable building blocks such as changing the size of their Λ-shape void and the dihedral angle (ca. up to 20°) of the scaffold.[29,31]

Compounds **6** and **7** are previously introduced as molecular photoswitches with the potential of being utilized for various purposes.[3] The strap modification can make the chirality of such compounds resistant to acids and tightens their scaffold which may be beneficial in molecule recognition studies. Therefore, the change of strap was herein performed on compound **7** to obtain its ethano-strapped derivative **9**. The strap-change operation (Scheme 3, step c) usually ends up with a mixture of both methano- and ethano-strapped TBAs, especially when TBAs carry electron-withdrawing groups. Despite many attempts, in optimizing the conversion of **7** into **9**, neither the higher ratio of alkyl halide–TBA nor elongated reaction time did improve the conversion yield beyond 30%. Also, the separation of these two is challenging because the butyl groups make the re-

tardation factors of **7** and **9** very close to one another. Hence, the separation of product **9** from the starting material **7** was a challenge for common liquid chromatography. Also, modifying a compound like **7** only gives a specialized product with specific properties which cannot be considered as a versatile building block. Therefore, as the ultimate goal of this project, a versatile and affordable building block had to be found, for example, a modified diamino TBA.



Scheme 3 Due to the symmetry of the products, they are presented as half. (a) (i) $H_2SO_4/NaNO_2$, (ii) 2, 6-dimethylphenol/Na_2CO_3; (b) C_4H_9Br/K_2CO_3; (c) $C_2H_4Br_2/Li_2CO_3$; (d) $Boc_{(anhyd)}/I_2$; (e) $C_2H_4Br_2/Li_2CO_3$; (f) (i) $H_2SO_4/NaNO_2$, (ii) 2,6-dimethylphenol/Na_2CO_3, (iii) C_4H_9Br/K_2CO_3; (g) H_2SO_4; (h) $Na_2S_2O_6$.

Although the reduction of **8** or **9** gives the desired ethano-strapped diamino building block **10** (Scheme 3, step h), such conversion is not convenient due to multiple steps and instability of **10**. A modified building block needs to be easily produced, stored, and be readily available for straightforward applications.

Having all these in mind, the preparation of **5** as an ethano-strapped versatile building block is reported in satisfactory yield without any of the aforementioned issues. In fact, the *N*-Boc-protected groups moderately activate the substrate compound **4** during the strap-change operation and also prevent the unwanted N-alkylation reactions.

Therefore, strap-change operation of **4** accomplished in good yields (up to 96% converted based on the crude's NMR, 77% isolated by chromatography). The obtained ethano-strapped TBA **5** can be readily unprotected and be converted into other functional groups as earlier performed on the methano-strapped analogues.

Exposure of diamino TBAs, for example, **10** (Table 1) and HB (Scheme 1), to air and light quickly decomposes them. This can be detected by the fast change of colour from white to brown. To prevent the decomposition, Boc protection of the amine groups was performed which significantly elongated the shelf life of these sensitive materials. The unprotection of **4** and **5** is fast and easy[32] and releases the corresponding diamino-TBAs which can be easily converted into the other desired compounds as described.

The generality of the applied methodologies are well documented in the literature, and rescaling the reactions up to tenfold showed not a considerable change of the yields percentage.

To conclude, a group of novel TBAs is safely prepared out of inexpensive materials. The illustrated structural modifications in this work can be considered as the reincarnation of this hundred-year-old compound. These novel products can be utilized as Λ-shape building blocks in the design of photonic crystals,[33] chiral ligands, receptors, catalysts, molecular machines, porous, and conductive[16,34] polymers.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588180. Detailed procedures and the NMR, MS, IR, and UV/Vis spectra are included.

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(35) **Synthesis and Characterization of Compound 1**
Hünlich's base (0.56 g, 2.0 mmol, 1.0 equiv) solution in H_2SO_4 (6.5%, 30 mL) was cooled down to –5 °C. A $NaNO_2$ solution (0.30 g, 4.4 mmol, 2.2 equiv in 5 mL cold H_2O) was dropped into the reaction flask and stirred for 30 min. The resulting yellowish solution was poured into a solution consisting *N*-benzylmethylamine (3 mL, excess), Na_2CO_3 (4.5 g), H_2O (60 mL), and MeCN (30 mL) chilled at –10 °C. The stirring was continued for 3 h meanwhile the temperature was gradually raised to r.t.; afterward, a beige precipitate was extracted from the aqueous mixture by CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 layers were combined, dried over Na_2SO_4, and filtered. The evaporation of the CH_2Cl_2 gave the crude product which was then purified by chromatography to furnish the purified bistriazene compound **1** as a light-yellow solid. Yield 0.65 g (1.2 mmol, 60%); R_f = 0.3 (silica gel; MeOH–CH_2Cl_2, 2% v/v). IR (neat): 3027, 2941, 2893, 2844, 1610, 1486, 1441, 1341, 1173, 1047, 921, 697 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.38 (m, 12 H, CH), 6.74 (s, 2 H, CH), 4.91–5.02 (q, *J* = 16.1 Hz, 4 H, NCH_2), 4.66–4.70 (d, *J* = 16.6 Hz, 2 H, CH_2), 4.36 (s, 2 H, NCH_2N), 4.22–4.26 (d, *J* = 16.8 Hz, 2 H, CH_2), 3.15 (b, 6 H, NCH_3), 2.30 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 146.3, 137.1, 129.0, 128.7, 128.6, 128.0, 127.7, 125.1, 112.7, 67.3, 58.8, 34.4, 17.2. MS (ESI$^+$; *i*-PrOH): *m/z* [M + H]$^+$ calcd for $[C_{33}H_{37}N_8]^+$: 545.31; found: 545.2. UV-vis: (EtOAc): λ (lg ε) = 297 (4.465) nm. Anal. Calcd for $C_{33}H_{36}N_8$: C, 72.77; H, 6.66; N, 20.57. Found: C, 72.56; H, 6.85; N, 20.18.
(36) **Synthesis and Characterization of Compound 2**
The bistriazene compound **1** (0.54 g, 1.0 mmol, 1.0 equiv) was poured into a 50 mL round-bottom flask containing CH_2Cl_2 (20 mL). A solution of trichloroacetic acid (5.0 g, 30 mmol, excess, in CH_2Cl_2 (20 mL)) was added and stirred for 2 min. Afterward, Na_2S (0.70 g, 9 mmol, excess) was slowly added to the reaction flask, as shown in the following figure, and remained sealed when stirred for 2 hours at r.t. The volume of the resulting yellowish suspension was then reduced to half by nitrogen gas flow and then refluxed for 30 min. The reaction mixture cooled down to r.t. and diluted with CH_2Cl_2 (100 mL), and filtered. The CH_2Cl_2 layer was rinsed with cold H_2O (5 × 100 mL), dried over Mg_2SO_4, and filtered. The CH_2Cl_2 was removed, and the residue was purified by column chromatography to obtain a pale-lemon substance with a mild rotten-egg odour which was then stored under argon in darkness. Yield 0.06 g (0.19 mmol, 19%); R_f = 0.2 (silica gel, MeOH–CH_2Cl_2, 4% v/v). IR (neat): 2896, 2847, 2560, 1608, 1492, 1474, 1205, 1091, 1010, 811 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.62 (br, 2 H, SH), 6.65 (s, 2 H, CH), 6.17 (s, 2 H, CH), 4.56–4.60 (d, *J* = 16.7 Hz, 2 H), 4.28 (s, 2 H, NCH_2N), 4.17–4.13 (d, *J* = 16.8 Hz, 2 H), 2.10 (s, 6 H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 134.5, 128.6, 127.4, 126.8, 124.7, 67.1, 58.4, 20.9. MS (ESI$^+$; *i*-PrOH–EtOAc–H_2O/0.5% HCO_2Na = 90:5:5): *m/z*

$[M + Na]^+$ calcd for $[C_{17}H_{18}N_2S_2Na]^+$: 337.08; found: 337.0. MS (ESI^-): *m/z* $[M - H]^-$ calcd for $[C_{17}H_{17}N_2S_2]^-$: 313.09; found: 313.1. MS (ESI^+; MeCN/Δ): *m/z* $[M + 2MeCN + H]^+$ calcd for $[C_{21}H_{25}N_4S_2]^+$: 397.14; found: 397.1. UV-vis: (EtOAc): λ (lg ε) = 277 (3.583) nm. Anal. Calcd for $C_{17}H_{18}N_2S_2$: C, 64.93; H, 5.77; N, 8.91; S, 20.39. Found: C, 65.08; H, 5.83; N, 9.22.

(37) **Synthesis and Characterization of Compound 3**

Hünlich's base (0.56 g, 2.0 mmol, 1.0 equiv) was dissolved in H_2SO_4 (6.5%, 90 mL), then cooled down to –5 °C. A $NaNO_2$ solution (0.30 g, 4.4 mmol, 2.2 equiv) in cold H_2O (10 mL) was dropped into the reaction flask and stirred for 30 min. Afterward, the solution's temperature was gradually raised to boil, over 2 h (attention: this step releases nitrogen gas; hence, rapid heating and sealing the container may lead to explosion). The reaction mixture was cooled down to r.t., its pH was adjusted to 5 (by adding Na_2CO_3 sat. solution) and extracted with EtOAc (5 × 30 mL), the organic layers were combined, dried over Na_2SO_4, and evaporated to dryness to obtain the product as a light-grey powder. Yield 0.54 g (1.9 mmol, 96%). R_f = 0.3 (silica gel, MeOH–CH_2Cl_2, 8% v/v). IR (neat): 3649, 3549, 3012, 2948, 2904, 2857, 1620, 1508, 1368, 1081, 910 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.06 (s, 2 H, OH), 6.56 (s, 2 H, CH), 6.45 (s, 2 H, CH), 4.39–4.43 (d, *J* = 16.4 Hz, 2 H, CH_2), 4.07 (s, 2 H, NCH_2N), 3.81–3.85 (d, *J* = 16.4 Hz, 2 H, CH_2), 1.97 (s, 6 H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 154.1, 146.5, 128.2, 119.9, 117.9, 110.0, 66.5, 57.8, 15.5. MS (ESI^+; EtOH–EtOAc–H_2O, 90:5:5): *m/z* $[M + H]^+$ calcd for $[C_{17}H_{19}N_2O_2]^+$: 283.14; found: 283.1. MS (ESI^-): *m/z* $[M - H]^-$ calcd for $[C_{17}H_{17}N_2O_2]^-$: 281.14; found: 281.1. UV-vis: (EtOAc): λ (lg ε) = 292 (3.643) nm. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; O, 11.33. Found: C, 72.21; H, 6.61; N, 9.74.