Useful Procedure for the Synthesis of Pincer-Type Heterodentate Azomethine Ligands Bearing Multiple Functionalities

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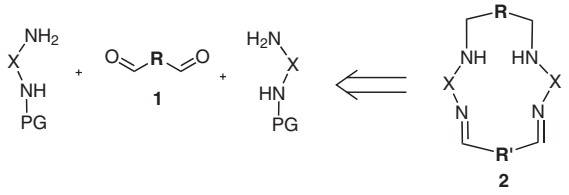
Abstract: A simple and efficient synthetic protocol is developed for the preparation of heterodentate azomethine ligands bearing various functionalities, by Schiff condensation of dialdehydes with monoprotected diamine followed by reduction of the azomethine bond and deprotection. The efficient procedure of obtaining *N*-*tert*-butoxycarbonyl-protected *o*-phenylenediamine in large scale is also elaborated.

Key words: Schiff bases, aromatic diamines, cyclizations, macrocycles, regioselectivity, heteropolydentate ligand

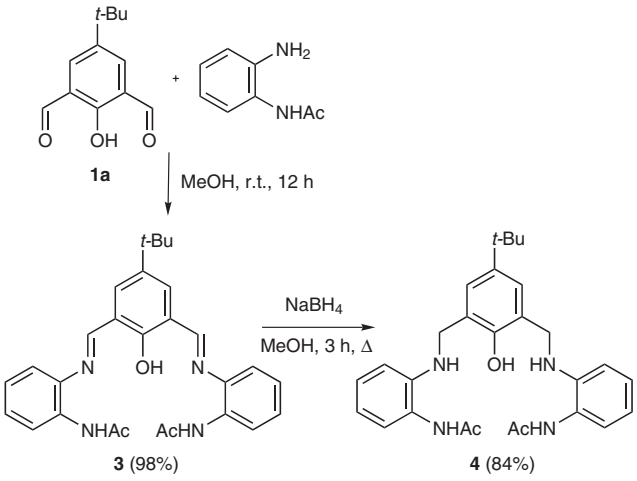
Pincer-type polyamines containing various functionalities are an important class of compounds in organic synthesis. They are of particular interest as useful building blocks for creating macrocyclic azomethines, which have found applications spanning from supramolecular recognition of metal ions,[1] anions,[2] and neutral molecules[3] to medical uses.[4]

Generally, construction of macrocyclic azomethines implies 'fragment-to-fragment' assembling[5,6] (Scheme 1). With this methodology, i.e., by condensation of preliminary monoprotected flexible aliphatic diamines with dicarbonyls **1** followed by reduction and deprotection, a number of macrocyclic derivatives **2** have been efficiently synthesized.[6] Unfortunately, due to the absence of sufficient conformational rigidity, the above type of macrocycles is not capable of acting as core of choice for selective supramolecular recognition.[6] Although the required level of conformational rigidity can be achieved by substituting aliphatic diamine units with aromatic analogues,[2c] no general method for obtaining macrocyclic azomethines bearing aromatic diamine units has been developed.



Scheme 1

Logically, if monoprotected aromatic diamines are used instead of aliphatic analogues at the stage of condensation with diformyls (Scheme 1), it will open a straightforward access to potentially very useful macrocyclic azomethines. Actually, in some preliminary investigations we observed that reaction of *N*-acetyl-*o*-phenylenediamine with diformylphenol **1a** in methanol smoothly led to 2:1-condensation product **3** which upon reduction with $NaBH_4$ gave the protected pincer diamine **4** in good overall yield (Scheme 2). Unfortunately numerous attempts to deprotect diamine **4** failed to be effective due to the unexpectedly high stability of amide bonds under both acidic and basic conditions. Thus, this paper describes a simple and short procedure of obtaining pincer-type enlarged aromatic diamines useful for further macrocyclic synthesis.



Scheme 2

The initial phase of our project required facile access to multigram quantities of *N*-*tert*-butoxycarbonyl-protected *o*-phenylenediamine **5**. The use of the latter building block for supramolecular chemistry was reported.[7] The traditional method for obtaining this useful block[7b] implies treatment of *o*-phenylenediamine with Boc-ON by utilizing large quantities of flammable solvents and carrying out the reaction by prolonged heating under anaerobic conditions.[7b] We proposed that substitution of Boc-ON with a more active Boc donor (e.g. Boc_2O) could make it possible to carry out the procedure under milder conditions. In support of this, Tamura et al. reported on the synthesis of **5** using Boc_2O. Unfortunately, neither experimental details nor the yield of target product were

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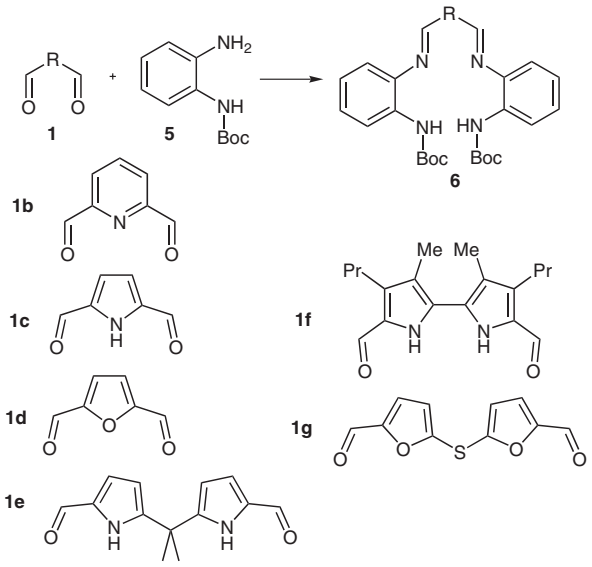
described.[8a] Heydari et al. reported the preparation of monoprotected diamine **5** in 80% yield by use of Boc_2O/$LiClO_4$ system, the reaction was carried out by stirring for five hours.[8b] In our hands, the use of Boc_2O allowed to reduce the reaction time down to ten minutes without necessity of exploring inert atmosphere, large volumes of flammable solvents and prolonged heating. Moreover, Boc_2O acts as efficient reagent at r.t. even when large quantities (45–75 g) of *o*-phenylenediamine were loaded and only subsequent crystallization was required to obtain pure monoprotected diamine **5** in satisfactory (69%) yield.

With a facile access to **5** in hand, a comparative study of obtaining Schiff bases **6** became real. In order to investigate the influence of electronic properties and topology of dicarbonyl compounds on the efficacy of Schiff base formation, a series of dicarbonyl derivatives was examined (Scheme 3, Tables 1 and 2). We chose to utilize **1b** which was expected to give good yield of Schiff base due to electron-withdrawing properties of pyridine nucleus. We also chose superaromatic pyrrolic derivatives **1c**, **1e** and **1f** which are known to form azomethines in low yields as well as their geometrical analogs, furan derivatives **1d**, **1g**, slightly exhibiting superaromaticity. 2,6-Diformyl-4-*tert*-butylphenol (**1a**) was selected by us as a model dicarbonyl derivative routinely used in obtaining Schiff bases.[1,5a,6b]



Scheme 3

In order to optimize the procedure of producing Schiff bases **6**, a broad variety of conditions was attempted. The best results were obtained when the reaction was carried out under mild conditions due to the possibility of suppressing thermal and oxidative degradation of starting dialdehydes. Thus, good yields of Schiff bases were obtained when condensations were performed by simple stirring of concentrated methanol solutions at room temperature for at least four hours (Scheme 3, Tables 1 and 2). In the cases of the slightly less reactive α-formyl pyrrolic derivatives **1c**, **1e**, and **1f**, acid catalyst (TsOH) was needed for obtaining the target products **6** in reasonable yields. In the absence of TsOH no target Schiff bases were isolated, the only result being 1:1 condensation products **7** (Figure 1) or a mixture of the corresponding Schiff bases **6** and **7**.

Table 1 Stepwise Synthesis of Diamine Blocks **9**

Dialdehyde	Yield of **6** (%)[a]	Yield of **8** (%)[a]	Yield of **9** (%)[a]
1a	70	98	90
1b	77	98[b]	75
1c	74[c]	76	–
1d	71	95	80
1e	70[c]	–[d]	–
1f	10[c]	–	–
1g	–[e]	–	–

[a] Yields refer to isolated products.
[b] Compound **8b** could be alternatively produced by reacting 2,6-bis(tosyloxymethyl)pyridine with *N*-*tert*-butoxycarbonyl-*o*-phenylenediamine.[9]
[c] Acid catalyst (TsOH, 0.1–0.3 molar equiv) is required.
[d] No **8e** was detected in the reaction mixture when the general procedure was used.
[e] No trace amounts of **6g** were isolated in the presence of TsOH, the only product (90%) being **7g**.

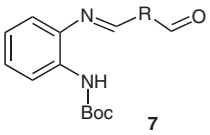


Figure 1 1:1 Condensation product **7**

In general, the efficacy of Schiff base formation correlates well with the electronic properties of the starting diformyls. When superaromatic diformylpyrroles **1c**, **1e**, and **1f** were used, acid catalyst was required to obtain the target Schiff bases, whereas furan analogue **1d** readily gave the desired **6d** in 71% yield without necessity of using catalyst. Surprisingly, only 1:1 condensation was observed when thiodiformylfuran derivative **1g** was used. We still cannot rationally explain this phenomenon.

To prepare *tert*-butoxycarbonyl protected amines, an efficient reduction of both azomethine bonds of Schiff bases **6** was required. We found that brief treatment of aldimines **6** with sodium borohydride in anhydrous methanol at room temperature gave the desired amines **8** in excellent yields (Scheme 4, Tables 1 and 2) whereas the use of traditional conditions (–30 °C) led to extensive degradation of target compounds. Unfortunately, we did not succeed in preparing even an analytical sample of dipyrrolic derivative **8f** due to its instability.

Table 2 Spectroscopic Data for Compounds **3**, **4**, **6**, **8**, and **9**

Product	IR (mull)	^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ
3[a,b]	1668 (C=O), 1622 (C=N), 3172 (OH), 3321 and 3390 (NH)	13.51 (s, 1 H, OH), 9.04 (s, 2 H, CH=N), 8.98 (br s, 2 H, NH), 8.25 (d, *J* = 7.2, 2 H_{arom}), 8.19 (s, 2 H_{arom}), 7.34 (d, *J* = 7.8, 2 H_{arom}), 7.28 (t, *J* = 7.8, 2 H_{arom}), 7.17 (t, *J* = 7.2, 2 H_{arom}), 2.17 (s, 6 H, CH_3), 1.42 (s, 9 H, *t*-C_4H_9)	167.88 (C=N), 159.42 (C=O), 141.96 (C_{arom}), 139.85 (C_{arom}), 135.96 (CH_{arom}), 133.41 (C_{arom}), 130.97 (CH_{arom}), 127.17 (CH_{arom}), 124.24 (CH_{arom}), 121.68 (CH_{arom}), 121.31 (CH_{arom}), 117.86 (C_{arom}), 34.04 (C), 30.05 (CH_3), 23.50 (CH_3)
4[c,d]	1680 (C=O), 3340 (NH, OH)	9.91 (br s, 1 H, OH), 7.75 (d, *J* = 5.7, 2 H_{arom}), 7.71 (d, *J* = 6.0, 2 H_{arom}), 7.47 (t, *J* = 5.7, 2 H_{arom}), 7.38 (t, *J* = 6.0, 2 H_{arom}), 7.29 (s, 2 H, NH), 5.69 (s, 4 H, NH_2), 2.92 (s, 6 H, CH_3), 1.12 (s, 9 H, *t*-C_4H_9)	152.15 (C=O), 143.76 (C_{arOH}), 132.13 (C_{arom}), 130.18 (CH_{arom}), 127.67 (C_{arom}), 126.09 (C_{arom}), 125.50 (C_{arom}), 124.32 (CH_{arom}), 114.16 (CH_{arom}), 113.63 (CH_{arom}), 45.44 (CH_2), 34.23 (C), 31.38 (CH_3) 23.37 (CH_3)
6a[c,e]	3385 (OH, NH), 1728 (C=O), 1685 (C=N), 1630 (C=NH)	13.85 (s, 1 H, OH), 8.97 (s, 2 H, NH), 8.56 (s, 2 H, HC=N), 8.09 (s, 2 H_{arom}), 7.67 (d, *J* = 7.6, 2 H_{arom}), 7.31 (t, *J* = 7.6, 2 H_{arom}), 7.25 (d, *J* = 7.6, 2 H_{arom}), 7. 18 (t, *J* = 7.6, 2 H_{arom}), 1.43 (s, 18 H, *t*-C_4H_9O), 1.36 (s, 9 H, *t*-C_4H_9)	159.61 (C=N), 154.35 (C=O), 153.24 (C_{arom}), 141.58 (C_{arom}), 141.33 (CH_{arom}), 133.13 (C_{arom}), 130.86 (CH_{arom}), 127.44 (CH_{arom}), 124.93 (CH_{arom}), 122.58 (CH_{arom}), 121.72 (CH_{arom}), 118.66 (C_{arom}), 79.61 (C), 34.21 (C), 31.43 (CH_3), 28.42 (CH_3)
6b[c,f]	3390 (NH), 1710 (C=O), 1610 (C=N), 1595 (CH_{arom})	8.72 (s, 2 H, NH), 8.40 (s, 2 H, HC=N), 8.37 (d, *J* = 8.0, 2 H_{arom}), 8.18 (t, *J* = 8.0, 1 H_{arom}), 7.91 (d, *J* = 8.0, 2 H_{arom}), 7.40 (d, *J* = 7.6, 2 H_{arom}), 7.29 (t, *J* = 8.0, 2 H_{arom}), 7. 12 (t, *J* = 7.6, 2 H_{arom}), 1.47 (s, 18 H, *t*-C_4H_9O)	159.87 (C=N), 154.52 (C=O), 139.77 (C_{arom}), 138.40 (C_{arom}), 133.75 (C_{arom}), 128.23 (CH_{arom}), 124.03 (CH_{arom}), 123.95 (CH_{arom}), 120.52 (CH_{arom}), 119.45 (CH_{arom}), 118.31 (CH_{arom}), 80.01 (C), 28.45 (CH_3)
6c	3400 (NH), 3310 (NH), 1730 (C=O), 1653 (C=N)	10.28 (br s, 1 H, NH), 8.37 (s, 2 H, HC=N), 8.22 (d, *J* = 8.0, 2 H_{arom}), 7.69 (s, 2 H, NH), 7.25 (t, *J* = 8.0, 2 H_{arom}), 7.06 (d, *J* = 7.6, 2 H_{arom}), 6.99 (t, *J* = 7.6, 2 H_{arom}), 6.82 (s, 2 H_{arom}), 1.55 (s, 18 H, *t*-C_4H_9O).	152.71 (C=O), 148.35 (C=N), 138.18 (C_{arom}), 134.69 (C_{arom}), 133.67 (C_{arom}), 127.57 (CH_{arom}), 122.56 (CH_{arom}), 118.25 (CH_{arom}), 117.34 (CH_{arom}), 116.88 (CH_{arom}), 80.64 (C), 28.35 (CH_3)
6d	3395 (NH), 1730 (C=O), 1620 (C=N), 1593 (CH_{arom})	8.49 (s, 2 H, HC=N), 8.25 (d, *J* = 8.3, 2 H_{arom}), 7.88 (s, 2 H, NH), 7.28 (t, *J* = 8.3, 2 H_{arom}), 7.24 (s, 2 H_{arom}), 7.17 (d, *J* = 7.8, 2 H_{arom}), 7.03 (t, *J* = 7.8, 2 H_{arom}), 1.56 (s, 18 H, *t*-C_4H_9O)	154.28 (C=O), 152.52 (C=N), 147.51 (C_{arom}), 138.95 (C_{arom}), 134.10 (C_{arom}), 128.03 (CH_{arom}), 123.51 (CH_{arom}), 119.10 (CH_{arom}), 119.02 (CH_{arom}), 117.68 (CH_{arom}), 79.98 (C), 28.15 (CH_3)
6e[c]	3380 (NH), 3216 (NH), 1729 (C=O), 1619 (C=N)	10.65 (br s, 2 H, NH), 8.03 (s, 2 H, HC=N), 7.96 (d, *J* = 7.5, 2 H_{arom}), 7.67 (br s, 2 H, NH), 7.14 (d, *J* = 7.1, 2 H_{arom}), 7.06 (t, *J* = 7.5, 2 H_{arom}), 6.97 (t, *J* = 7.1, 2 H_{arom}), 6.59 (br s, 2 H_{arom}), 6.01 (br s, 2 H_{arom}), 2.76 (s, 6 H, CH_3), 0.94 (s, 18 H, *t*-C_4H_9O)	152.71 (C=O), 150.39 (C=N), 146.33 (C_{arom}), 138.51 (C_{arom}), 133.91 (C_{arom}), 130.34 (CH_{arom}), 126.44 (CH_{arom}), 122.15 (CH_{arom}), 119.77 (CH_{arom}), 119.38 (CH_{arom}), 118.38 (CH_{arom}), 108.05 (C_{arom}), 79.86 (C), 50.22 (C), 36.26 (CH_3), 27.42 (CH_3)
6f[g]	3482 (NH), 3380 (NH), 1723 (C=O), 1610 (C=N), 1580 (CH_{arom})	9.28 (br s, 2 H, NH), 8.35 (s, 2 H, HC=N), 8.12 (d, *J* = 7.6, 2 H_{arom}), 7.75 (s, 2 H, NH), 7.21 (t, *J* = 7.6, 2 H_{arom}), 7.3–6.8 (m, 4 H_{arom}), 2.66 (t, *J* = 7.8, 4 H, CH_2), 2.19 (s, 6 H, CH_3), 1.64 (dd, *J* = 8.0, 7.8, 4 H, CH_2), 1.48 (s, 18 H, *t*-C_4H_9O), 1.02 (t, *J* = 8.0, 6 H, CH_3)	152.53 (C=O), 146.05 (C=N), 133.43 (C_{arom}), 132.59 (C_{arom}), 127.90 (CH_{arom}), 126.43 (CH_{arom}), 122.31 (CH_{arom}), 118.63 (CH_{arom}), 117.62 (C_{arom}), 116.38 (C_{arom}), 80.21 (C), 28.26 (CH_3), 25.99 (CH_2), 24.69 (CH_3), 13.94 (CH_2), 10.12 (CH_3)
8a[h]	3330 (NH), 1700 (C=O), 1605 (CH_{arom})	8.76 (br s, 1 H, OH), 7.36 (d, *J* = 6.8, 2 H, CHar), 7.21 (s, 2 H_{arom}), 7.11 (t, *J* = 7.6, 2 H_{arom}), 7.0–6.7 (m, 4 H_{arom}), 6.36 (br s, 2 H, NH), 4.37 (s, 4 H, CH_2), 1.50 (s, 18 H, *t*-C_4H_9), 1.32 (s, 9 H, *t*-C_4H_9).	154.11 (C=O), 152.81 (COH), 142.43, (C_{arom}) 141.31 (C_{arom}), 126.27 (CH_{arom}), 125.59 (CH_{arom}), 124.80 (CH_{arom}), 123.73 (C_{arom}), 119.83 (CH_{arom}), 114.72 (CH_{arom}), 80.55 (C), 46.74 (CH_2), 34.05 (C), 31.52 (CH_3), 28.25 (CH_3)
8b	3423, 3325 (NH), 1695 (C=O), 1595 (CH_{arom})	7.56 (t, *J* = 7.6, 1 H_{arom}), 7.29 (d, *J* = 7.2, 2 H_{arom}), 7.16 (d, *J* = 7.6, 2 H_{arom}), 7.063 (t, *J* = 7.6, 2 H_{arom}), 6.73 (t, *J* = 7.2, 2 H_{arom}), 6.67 (d, *J* = 7.6, 2 H_{arom}), 4.45 (s, 4 H), 1.43 (s, 18 H)	157.41 (C=O), 142.45 (C_{arom}), 137.26 (C_{arom}), 126.90 (CH_{arom}), 126.10 (CH_{arom}), 124.22 (C_{arom}), 120.16 (CH_{arom}), 117.89 (CH_{arom}), 112.70 (CH_{arom}), 80.57 (C), 49.13 (CH_2), 28.32 (CH_3)

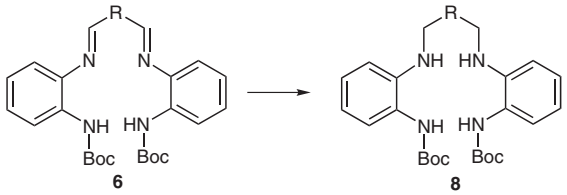
Table 2 Spectroscopic Data for Compounds **3**, **4**, **6**, **8**, and **9** (continued)

Product	IR (mull)	^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ, *J* (Hz)	^{13}C NMR (100 MHz, $CDCl_3$/TMS) δ
8d	–	7.33 (d, *J* = 7.6, 2 H_{arom}), 7.05 (t, *J* = 7.6, 2 H_{arom}), 6.8–6.5 (m, 4 H_{arom}), 6.39 (br s, 2 H, NH), 6.13 (s, 2 H_{arom}), 4.22 (s, 4 H, CH_2), 1.49 (s, 18 H, *t*-C_4H_9O)	151.99 (C=O), 126.19 (C_{arom}), 124.86 (C_{arom}), 122.38 (C_{arom}), 118.83 (CH_{arom}), 116.51 (CH_{arom}), 113.27 (CH_{arom}), 109.84 (CH_{arom}), 107.91 (CH_{arom}), 80.47 (C), 41.74 (CH_2), 28.33 (CH_3)
9a[i]	3320 (NH_2, NH), 1600 (CH_{arom})	7.23 (s, 2 H_{arom}), 7.1–6.7 (m, 8 H_{arom}), 4.39 (s, 4 H, CH_2), 1.32 (s, 9 H, CH_3)	153.65 (COH), 135.49 (C_{arom}), 125.85 (CH_{arom}, C_{arom}), 123.76 (C_{arom}), 120.44 (CH_{arom}), 116.48 (CH_{arom}), 113.93 (CH_{arom}), 110.74 (CH_{arom}), 46.80 (CH_2), 34.21 (C), 31.50 (CH_3)
9b	3360 (NH_2, NH), 1595, 1578 (CH_{arom})	7.52 (t, *J* = 7.6, 1 H_{arom}), 7.17 (d, *J* = 7.6, 2 H_{arom}), 6.78 (td, *J* = 7.6, 1.6, 2 H_{arom}), 6.73 (dd, *J* = 7.6, 1.6, 2 H_{arom}), 6.66 (td, *J* = 7.6, 1.3, 2 H_{arom}), 6.62 (dd, *J* = 7.6, 1.3, 2 H_{arom}), 4.43 (s, 4 H, CH_2), 4.25 (br s, 6 H, NH_2, NH)	157.71 (C), 137.38 (CH_{arom}), 133.74 (C_{arom}), 121.04 (CH_{arom}), 120.31 (CH_{arom}), 118.96 (CH_{arom}), 117.02 (CH_{arom}), 112.44 (CH_{arom}), 49.39 (CH_2)
9d	–	6.81 (td, *J* = 7.6, 1.5, 2 H, CH), 6.76 (dd, *J* = 7.6, 1.5, 2 H, CH), 6.70 (dd, *J* = 7.6, 1.2, 2 H, CH), 6.66 (td, *J* = 7.6, 1.2, 2 H, CH), 6.12 (s, 2 H, CH), 4.46 (s, 4 H, CH_2), 4.28 (br s, 6 H, NH)	157.71 (C_{arom}), 137.37 (C_{arom}), 133.73 (C_{arom}), 121.03 (CH_{arom}), 120.30 (CH_{arom}), 118.95 (CH_{arom}), 117.00 (CH_{arom}), 112.42 (CH_{arom}), 49.37 (CH_2)

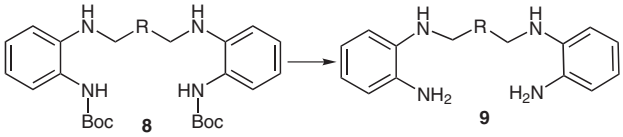
[a] ^{1}H and ^{13}C NMR data were obtained in acetone-d_6.
[b] Mp 193–194 °C (MeOH). Anal. Calcd for $C_{28}H_{30}N_4O_3$: C, 71.47; H 6.43; N, 11.91. Found: C, 71.44; H, 6.48; N, 11.94.
MS (EI): *m*/*z* (%) = 469 (100, [M – H^+]), 440 (35, [M – 2 CH_3^+]), 427 (75, [M – 3 CH_3^+]), 383 (20, [M – 2 Ac – H^+]).
[c] ^{1}H and ^{13}C NMR data were obtained in DMSO-d_6.
[d] Mp 198–199 °C (EtOH). Anal. Calcd for $C_{28}H_{32}N_4O_3$×2 HCl×H_2O: C, 59.68; H, 6.44; N 9.94. Found: N, 59.44; C, 6.34; N, 9.51. MS (EI): *m*/*z* (%) = 308 (27, [M – $C_9H_{13}N_2O^+$]), 150 (75, [$H_2NC_6H_4NHAc^+$]), 132 (100, [$C_6H_5NHAc^+$]), 108 (70, [$H_2NC_6H_4NH^+$]), 43 (35, [C_3H_7]$^+$).
[e] Mp 210–212 °C (MeOH). Anal. Calcd for $C_{34}H_{42}N_4O_5$: C, 69.60; H, 7.22; N, 9.55. Found: C, 69.57; H, 7.11; N, 9.45. MS (MALDI-TOF): *m*/*z* = 587 (100, [M + H^+]).
[f] Mp 159–160 °C (MeOH). Anal. Calcd for $C_{29}H_{33}N_5O_4$: C, 67.55; H, 6.45; N, 13.58. Found: C, 67.45; H, 6.37; N, 13.27.
[g] Anal. Calcd for $C_{40}H_{52}N_6O_4$: C, 70.56; H, 7.70; N, 12.34. Found: C, 71.24; H, 7.72; N, 12.16.
[h] Anal. Calcd for $C_{34}H_{46}N_4O_5$: C, 69.13; H, 7.85; N, 9.48. Found: C, 69.35; H, 7.88; N, 9.27.
[i] Mp 75–77 °C (MeOH–H_2O). Anal. Calcd for $C_{24}H_{30}N_4O$: C, 73.81; H, 7.74; N, 14.35. Found: C, 73.61; H, 7.93; N, 14.18.

Target diamine blocks **9** were produced by deprotecting amines **8** with gaseous HCl in anhyd dichloromethane (Scheme 5, Tables 1 and 2) followed by brief treatment with 10% aqueous Na_2CO_3 solution. The above conditions were found to be optimal due to high yields of the desired diamines **9**. In addition, usual workup is actually very simple and requires only evaporation of the solvents. We observed that free amines **9** are prone to undergo spontaneous oxidation on contact with air. In view of the above mentioned instability, target diamines **9** can be fixed in the form of stable dihydrochlorides if no treatment with Na_2CO_3 is carried out at the stage of deprotecting amines **8**.

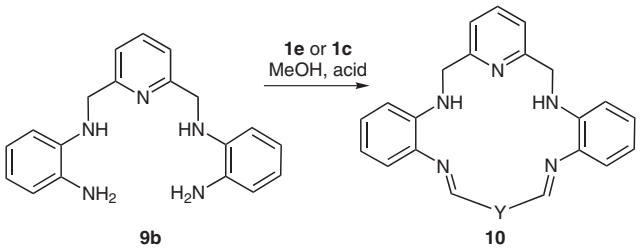
The final objective of our studies was to demonstrate the possibility of using diamine blocks in creating macrocyclic Schiff bases. In order to obtain unsymmetrical macrocycles bearing hard and soft donor centers we treated block **9b** with various pyrrolic dialdehydes in methanol (Scheme 6). Due to low activity of the starting diformyls **1c** and **1e**, an acid catalyst was required (vide supra) to provide efficient macrocyclization. When **9b** was treated with diformyldipyrrolylmethane **1e**, the expected product **10a** of 1:1 macrocyclization was isolated and characterized by both ^{1}H and ^{13}C NMR and mass spectrometry. Interesting results were obtained when diformylpyrrole **1c** was introduced into the reaction with **9b**. Thus, according to MALDI-TOF spectra of the crude reaction mixture, no peak corresponding to target macrocycle **10b**[10] was detected, the main peak being due to unexpected 2:2-cyclocondensation product. We also observed that the above product is an unstable compound which is prone to give oligomers when attempts were made to isolate it in pure form.



Scheme 4



Scheme 5



Scheme 6

In summary, we have developed a simple and efficient method of producing polyamines which can be utilized as useful synthons for creating functionally substituted macrocycles. The key advantage of this approach is the small number of stages (three) and good overall yields. Coupled with availability of starting dicarbonyl compounds and monoprotected diamine, it affords additional synthetic benefits for constructing novel macrocycles. We are currently investigating the flexibility of this method to prepare novel macrocyclic derivatives by means of varying aromatic diamines and dicarbonyl components.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer at 24 °C. IR spectra were determined on a Nicolet FT-IR spectrometer. Mass spectra were performed on a MALDI-TOF Reflex 3 instrument (Bruker) in the positive ion mode (UV laser, 337 nm) and on a Finnigan MAT 212 instrument; the energy of ionizing electrons was 70 eV; the temperature of the ionization chamber was 230 °C.

The starting compounds were synthesized by literature methods: **1a**,[11] **1b**,[12] **1c**,[13] **1d**,[14] **1e**,[15] **1g**[16] and *N*-acetyl-*o*-phenylenediamine.[17] A sample of diformyl **1f** was a gift from Mr. Nikolai V. Boev (M. V. Lomonosov Moscow State University).

Schiff Base 3

To solution of *N*-acetyl-*o*-phenylenediamine (1.455 g, 9.7 mmol) in anhyd MeOH (7 mL) was added dropwise a solution of **1a** (1 g, 4.85 mmol) in anhyd MeOH (7 mL). The mixture was stirred for 8 h at r.t. Product **3** was collected by filtration. An additional portion of the substance was obtained by the partial evaporation of the filtrate to give 2.24 g (98%) of **3** (Table 2).

Pincer-Type Amine 4

To a cooled (0 °C) solution of **3** (5.0 g, 10.65 mmol) in EtOH (150 mL) was added portionwise $NaBH_4$ (1.62 g, 42.6 mmol) over 1.5 h. The mixture was stirred for 2 d, and then treated with solution of NaOH (3.5 g) in H_2O (12.5 mL). The product was extracted with $CHCl_3$ (2 × 100 mL). The organic extracts were dried (Na_2SO_4) and evaporated to dryness. The resulting oil was treated with a large excess of concd HCl (10 mL). Then the dihydrochloride salt of **4** was purified by recrystallization from EtOH to give 4.23 g (84%) of pure **4**·2HCl·H_2O (Table 2).

***N-tert*-Butoxycarbonyl-*o*-phenylenediamine (5)**

To a solution of *o*-phenylenediamine (30 g, 278 mmol) in 1,4-dioxane (900 mL), H_2O (60 mL), concd HCl (48 mL) and additional portion of H_2O (30 mL) were successively added. Then Boc_2O (60.6 g, 278 mmol) was added and the solution was stirred at r.t. for 10 min. Solid $NaHCO_3$ (70 g, 834 mmol) was added and the solution was thoroughly triturated and evaporated to dryness under reduced pressure. The precipitate so-obtained was extracted with $CHCl_3$ (300–400 mL). NaCl was filtered out and the solution was brought to 40–50 °C. Then hexane was slowly added until the solution became slightly turbid. Upon cooling, the precipitate which formed was filtered out to give 40 g (69%) of **5**.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53 (s, 9 H, *t*-C_4H_9), 3.81 (br s, 2 H, NH_2), 6.36 (br s, 1 H, NH), 6.9–6.7 (m, 2 H, CH), 7.00 (td, 1 H, *J* = 7.7, 1.5 Hz, CH), 7.28 (d, *J* = 7.6 Hz, CH).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 28.29 (CH_3), 80.44 (C), 117.55 (CH), 119.56 (CH), 124.77 (CH), 126.07 (CH), 126.94 (C), 139.85 (C), 153.87 (C=O).

Schiff Bases 6a–f; General Procedure

To a solution of **1a–g** (1 mmol) in a minimum quantity of anhyd MeOH (10–30 mL) was added **5** (416 mg, 2 mmol) (a few crystals of PTSA were also added when compounds **1c**, **1e**, and **1f** were loaded) and the mixture was stirred at r.t. The reaction was monitored by analytical TLC (eluent EtOAc–petroleum ether, 1:1). After filtration of the target compounds **6a–f**, the filtrate was evaporated to dryness and the precipitate so-obtained was purified by chromatography on silica gel (EtOAc–petroleum ether, 1:1) to give additional portions of **6a–f** (Tables 1 and 2).

Protected Pincer-Type Ligands 8a–d; General Procedure

To a suspension of **6** (0.3 mmol) in anhyd MeOH (10 mL), was added $NaBH_4$ (38 mg, 1.0 mmol) and mixture was stirred for 3 h. It was then concentrated in vacuo, diluted with CH_2Cl_2 (25 mL), and filtered through a short silica column. Evaporation of the solvents gave the respective **8a–d** (Tables 1 and 2).

Pincer-Type Diamines 9a, 9b, 9d; General Procedure

Stream of dry HCl was bubbled through a solution of **8** (0.1 mmol) in anhyd CH_2Cl_2 (20 mL). After 40 min, the precipitate formed was treated with 10% aq solution of Na_2CO_3 to pH >7. The organic layer was dried (K_2CO_3) for 6 h and solvent was removed under reduced pressure to give the respective **9a**, **9b**, **9d** (Tables 1 and 2).

Macrocycle 10a; Typical Procedure

To a solution of **9b** (32 mg, 0.1 mmol) and **1e** (2.3 mg, 0.1 mmol) in anhyd MeOH (10 mL), was added one drop of H_3PO_4 (70% aq). After stirring overnight, anhyd Et_3N (1 mL) was added and the precipitate was filtered out. The solvent and excess of Et_3N were evaporated in vacuo and the residue was purified by flash chromatography on alumina Brockmann grade II (elution with CH_2Cl_2–MeOH, 95:5) to give 46 mg (90%) of **10a** as a yellow powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.01 (s, 2 H, NH), 7.72 (d, *J* = 8.1 Hz, 2 H, CH), 7.3–7.0 (m, 6 H, CH), 6.84 (d, *J* = 7.6 Hz, 2 H, CH), 6.54 (br s, 2 H, CH), 6.14 (br s, 2 H, CH), 5.18 (s, 4 H, CH_2), 1.72 (s, 6 H, CH_3).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 155.82 (C=N), 148.09 (C), 142.97 (C), 142.2 (C), 138.2 (C), 135.57 (C), 122.46 (CH), 120.77 (CH), 120.21 (CH), 119.35 (CH), 116.66 (CH), 113.27 (CH), 108.70 (CH), 106.36 (CH), 46.03 (CH_2), 30.30 (C), 10.78 (CH_3).

MALDI-TOF: *m*/*z* (%) = 510 (M – 3 H^+, 100), 1024 [$(M – H)_2^+$, 10].

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