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Synthesis of side-chain functionalised ligands for the generation of quartet receptor arrays via self-assembly of [2×2] grid complexes

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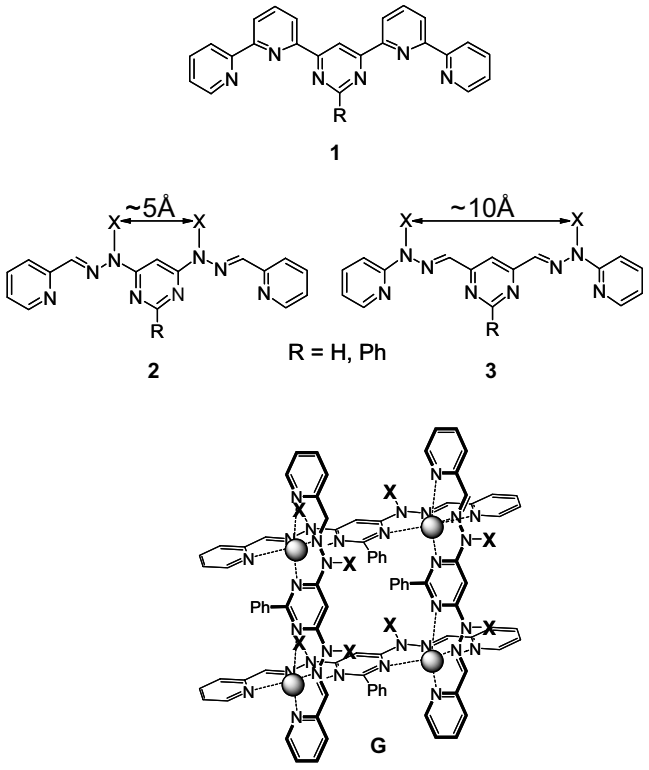
Abstract—The decoration of bishydrazone compounds of types **2** and **3** by attachment of various side chains, in particular of biological nature, yields a set of functionalised ligands. Their self-assembly with zinc(II) and cobalt(II) ions into [2×2] grids provides an approach towards nanosized metallosupramolecular architectures presenting quartet receptor arrays of interest for the development of nanosized biochips.

The self-assembly of metallosupramolecular architectures of wide structural diversity from multidentate ligands directed by appropriate metal ions has been a subject of intense activity.[1–8] In particular, grid-like complexes have been considered as potential arrays for high-density information storage,[2f,3a,7] especially in the case of heterometallic species presenting different metal ions in well-defined arrangement.[8] Furthermore, such entities exhibit unique physico-chemical properties of magnetic,[2a–e] redox[3] and optical[4] nature, which might be of use for sensing and signalling devices based on magnetic, electrochemical[5] or optical[4a] changes.

Following extensive work with ligands of bis-bipyridine type **1**,[6,7] our group reported recently about the design of bis-hydrazone analogs **2** and **3** as easily synthesised bis(tridentate) ligands for the construction of [2×2] grid arrays (Scheme 1).[4b,8b] Such bis-hydrazone ligands carry ionisable N–H sites (X = H) on the hydrazone moiety, resulting in neutral [2×2] grid architectures **G** (X = –) on self-assembly with divalent metal cations (Scheme 1). Most significantly, these nitrogens should allow the



Scheme 1. Bis(tridentate) ligands **1**–**3** for the self-assembly of [2×2] grid metalloarrays based on bisbipyridine (**1**) and bispyridylhydrazone (**2**, **3**) scaffolds, and [2×2] grid-type architecture **G** resulting from self-assembly of **2** with divalent metal cations M = ●, X: sites of functionalisation. The ligands are represented in the conformation presenting the two metal ion coordination sites.

Keywords: Functionalised ligands; Grid complexes; Nanobiochips; Receptors; Supramolecular chemistry.
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attachment of a variety of functional groups X, which may alter or fine-tune the properties of the grid complexes.

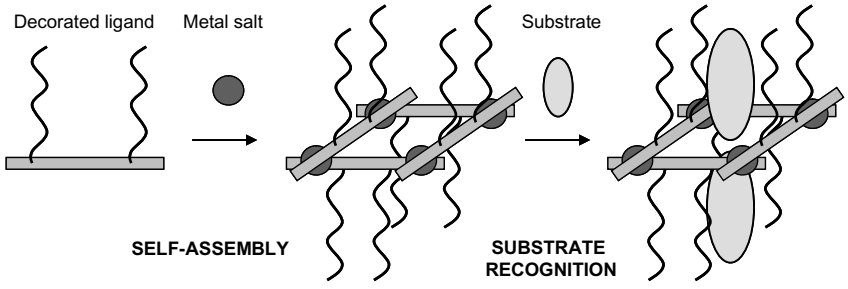
On the other hand, grid formation will result in the presentation of a quartet array of X residues, in a receptor pocket-like fashion, on each side of the grid, which thus serves as self-assembling scaffold of well-defined geometry. In addition, these pockets exhibit different sizes depending on the ligand structure, as the distance between the sites of functionalisation is about 5 Å for ligand **2** and 10 Å for ligand **3**. Binding of a substrate into these quartet sites may be expected to induce a change in magnetic,[2a–e] electrochemical[5] or optical[4] properties, thus resulting in a sensing event (Scheme 2).

Towards these goals, the first crucial step is the functionalisation of the bishydrazone ligands **2** and **3** by attaching different substituents, in particular of biological nature, to the ionisable nitrogen sites. We now report some of our results on the synthesis of such ligands **4**–**6** (Scheme 3) and on their ability to form [2×2] grid assemblies with appropriate metal ions.

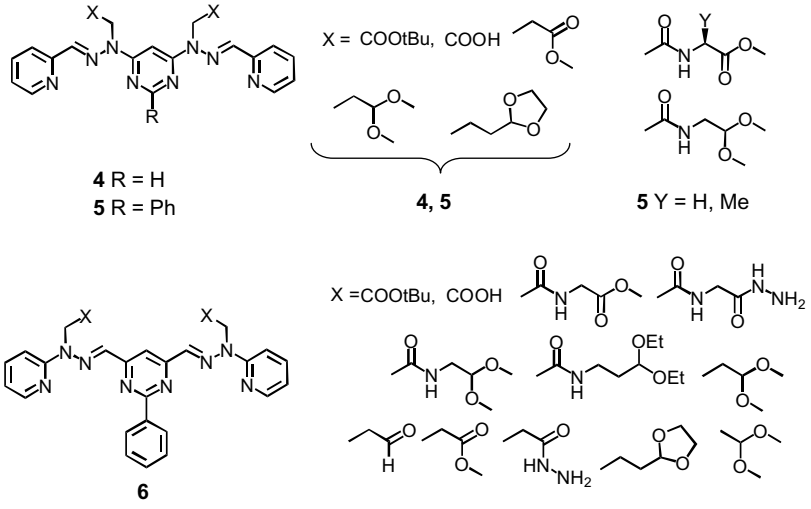
Two different synthetic strategies were developed, both based on the nucleophilic substitution of alkyl halides using the recently reported[4b] ionisable bishydrazone ligands **2** and **3** as nucleophiles.[9] Depending on the structure envisaged, the substitution reaction was performed, either by applying a mild base like potassium carbonate in DMF or by using a strong base like butyllithium in THF. The desired functionalised substances could be obtained in moderate overall yield independently of the ligand scaffold **2** or **3**. Scheme 4 summarises some of the synthetic procedures employed. The compounds were characterised by spectrometric (NMR, mass) and analytic methods.

Of special interest is the introduction of carboxylic ester groups as well as of carbonyl or hydrazide functions (see Schemes 3 and 4). The former allow the attachment of amino acid residues through amide linkages. The latter give access to further decoration by reversible C=N bond formation via dynamic combinatorial chemistry[10] processes. One may note that ligands such as **5c**, **5c′** and **6d** bear dipeptide type chains (GlyGly for **5c**, **6d** and GlyAla for **5c′**).

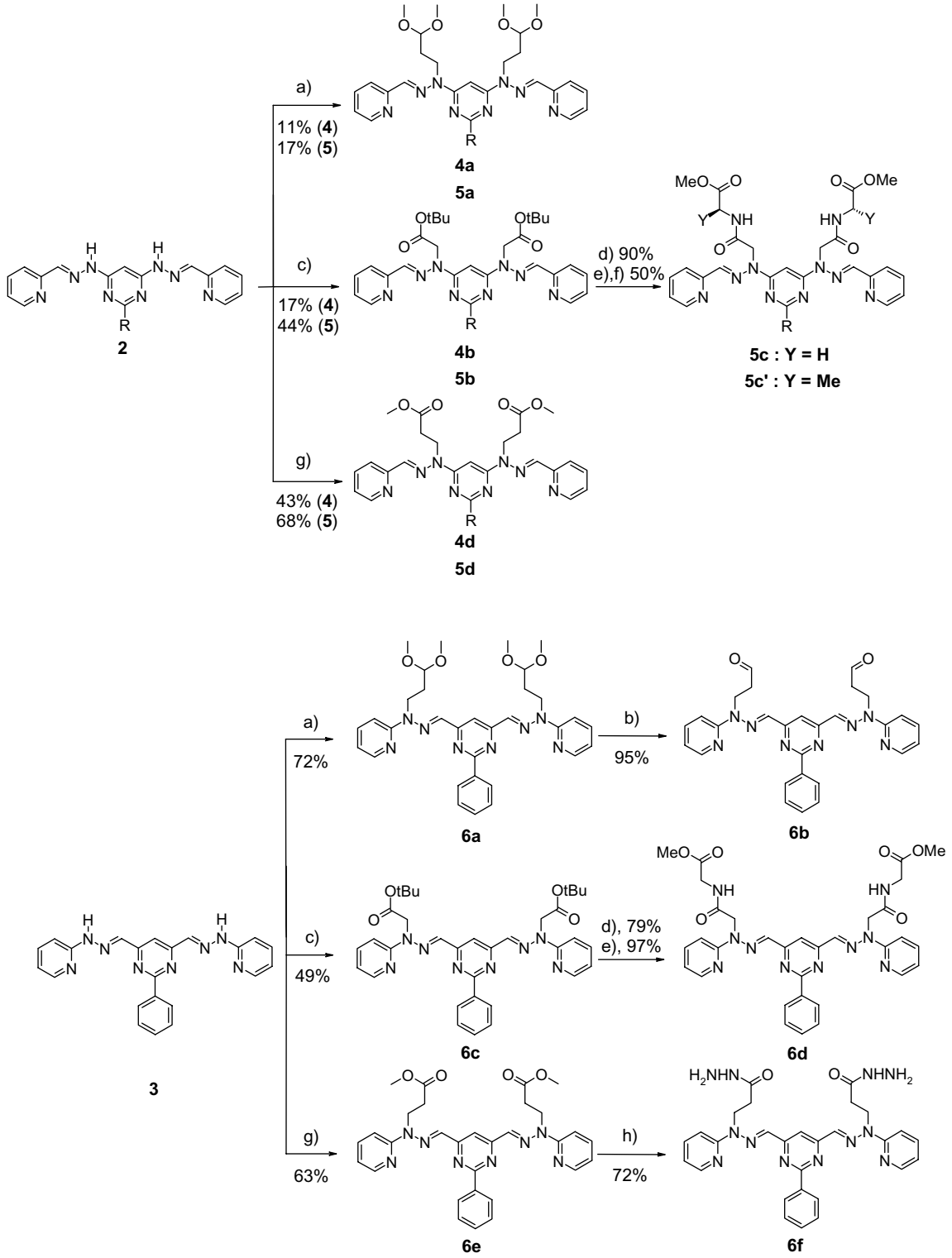
With these ligands in hand, the self-assembly into [2×2] grid architectures was explored.[11] The formation of these square metalloarrays with appropriate metal ions was not straightforward and failed in some instances. Some general trends were observed concerning the grid-forming ability of the different ligands of structure



Scheme 2. Schematic representation of the self-assembly of functionalised grid-type architectures presenting two quartet receptor arrays for subsequent substrate binding.



Scheme 3. Functionalised bishydrazone ligands **4**–**6** which have been synthesised.



Scheme 4. Synthesis of functionalised ligands. (a) 3-Bromopropionaldehyde dimethyl acetal, K_2CO_3, NaI, DMF, 110 °C; (b) acetone, 10% HCl, rt; (c) *tert*-butyl bromoacetate, 1.6 M BuLi in hexane, THF, −78 °C–rt; (d) CF_3COOH, CH_2Cl_2, rt; (e) glycine methyl ester hydrochloride, EDC, HOBt, Et_3N, THF, 0 °C–rt; (f) L-alanine methyl ester hydrochloride, EDC, HOBt, Et_3N, THF, 0 °C–rt; (g) methyl 3-bromopropionate, K_2CO_3, NaI, DMF, 110 °C; (h) hydrazine hydrate, EtOH, Δ.

4–6. First, the ligands carrying the ionisable nitrogens on the pyrimidine moiety **4**, **5** form [2×2] grid complexes in all cases, those of type **5** (R = Ph) showing the highest tendency to assemble, in line with the earlier work on grid formation with ligands of type **1** (R = Ph).[6a–c,7] Secondly, the ligands **6** presenting the hydrazone groups linked to the pyridine moieties, were more reluctant to form [2×2] grids. Although not all combinations were tried out, the formation of the following complexes was confirmed by spectrometric (NMR, mass) methods

(ligand, metal ion): (**4a**, Co^{II}), (**4d**, Zn^{II}), (**5a**, Zn^{II}), (**5b**, Zn^{II}), (**5c**, Zn^{II}), (**5c′**, Zn^{II}), (**6c**, Zn^{II}), (**6e**, Zn^{II}; **6e**, Co^{II}).

After elaborating these general effects, we next focused on ligand systems carrying substituents of special interest for dynamic combinatorial chemistry[10] and of biological relevance. Thus, we tried to assemble the aldehyde-functionalised ligand **6b**, for example, into a grid architecture with zinc(II), cobalt(II) and iron(II) ions, but it was not possible to obtain any grid structure as verified by NMR and ESMS analysis.

Protected aldehyde-bearing ligands were then considered, since this would not preclude the creation of a dynamic combinatorial library after deprotection. Indeed, acetal-functionalised ligands did form [2×2] grid complexes in several instances, although in the conditions used, clean assembly of these architectures was only obtained for ligands **4a** and **5a** of type **2** (Scheme 4). These complexes will allow the reversible decoration with biological residues by reaction with amino-functionalised biomolecules such as amino acids, etc.[12]

Next, the irreversible attachment of biomolecules was envisaged.[13] The functionalisation with glycine methyl ester and L-alanine methyl ester via amide bonds as model compounds resulted in peptoid ligand structures **5c**, **5c′**, **6d** (Scheme 4). The treatment of these ligands with appropriate metal ions (Zn^{II}, Co^{II}) allowed the characterisation of the expected [2×2] grid architectures **G** (X = side group), as unambiguously indicated by NMR and ESMS analysis.

The attachment of functional groups, in particular of biological nature, onto the bis(tridentate) bishydrazone ligands **2**, **3** and the subsequent assembly into [2×2] grid-like complexes gives access to the generation of self-assembled chip-type devices of nanometric size, bearing residues connected in either an irreversible or a reversible fashion. Immobilisation of biomolecules is thus achieved resulting in an assembly presenting two recognition pockets defined by quartet arrays of biological residues on both sides of the grid architectures. Further, the two ligand systems **4**, **5** and **6** provide the possibility to alter the distance between the biological residues and to tailor the receptor sites of the nanosized bio-arrays to the size of the substrate(s).

The present proof of principle may be extended to other biomolecules such as oligonucleotides, oligopeptides or oligosaccharides.[12,13] Further, this methodology should be transferable to larger grid assemblies like [3×3][14] or [4×4] grid structures,[15] allowing potentially the immobilisation of up to 32 bio-residues. One may also consider the attachment of the functional groups *after* the assembly of the unsubstituted ligands into grid-like metalloarrays, as has been realised for simple mononuclear iron complexes of hydrazone ligands.[16]

In conclusion, we have synthesised a variety of differently *N*,*N*′-bisfunctionalised bishydrazone ligands **4**–**6** and examined their ability to form [2×2] grid assemblies by coordination of metal ions like zinc(II) or cobalt(II). These grid assemblies represent the first step towards nano-biochips, in which different biomolecules are immobilised on a grid 'surface', in reversible or irreversible fashion. Further work is aimed at the extension towards larger grid architectures, the development of other decoration methodologies,[9] and the attachment of other types of functionalised moieties, as well as the exploration of more biocompatible reaction conditions. Such investigations provide access to the generation of self-organised nano-architectures of interest for the multivalent presentation of biological residues,[17] for the development of biochip array technology[18,19] and for the design of nanosensors.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.07.034.

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11. Synthesis of [2×2] grid-type complexes: $Zn_4(\mathbf{5c})_4(OTf)_8$: To a stirred solution of 13.9 mg (38.3 μmol) zinc(II) triflate in 2 mL acetonitrile was added 25.0 mg (38.3 μmol) bishydrazone ligand **5c**. After stirring the yellow solution overnight, the [2×2] grid complex was precipitated as a red solid with diisopropylether. Yield: 18.7 mg (4.6 μmol, 48%). Analytical data: ^{1}H NMR (acetonitrile-d_3, 400 MHz): δ (ppm) 1.09, 3.65, 4.08, 4.70, 5.47, 5.88, 6.59, 6.75, 7.30, 7.67, 7.72, 7.91, 7.97, 8.17, 8.26; ESMS: 1205, $Zn_4(\mathbf{5c})_4(OTf)_5^{3+}$.
$Zn_4(\mathbf{5c}')_4(OTf)_8$: This complex was prepared in the same way as the previous one; ^{1}H NMR (acetonitrile-d_3, 400 MHz): δ (ppm) = 1.50 (d, 6H, H-20), 3.53 (s, 3H, H-19), 3.67 (s, 3H, H-19′), 4.45 (m, 2H, H-17), 4.65 (m, 2H, H-6), 5.42 (m, 2H, H-6′), 5.85 (d, 1H, H-12), 6.58 (d, 1H, H-12′), 6.74 (s, 1H, H-9), 7.32 (m, 3H, H-3, H-13), 7.66 (m, 3H, H-1, H-13′), 7.92 (m, 2H, H-2), 8.01 (s, 2H, H-7), 8.18 (m, 2H, H-4), 8.26 (m, 1H, H-14). ES-MS: 894.9 ($Zn_4(\mathbf{5c}')_4(OTf)_4^{4+}$), 1242 ($Zn_4(\mathbf{5c}')_4(OTf)_5^{3+}$).
For proton numeration see compounds **5c** and **5c′** in Supplementary Material.
$Co_4(\mathbf{6a})_4(BF_4)_8$: To a stirred solution of 10.3 mg (30.2 μmol) cobalt(II) tetrafluoroborate hexahydrate in 2 mL acetonitrile was added 18.1 mg (30.2 μmol) bishydrazone ligand **6a**. After stirring the red solution overnight, the [2×2] grid complex was precipitated as red solid with diisopropylether. Yield: 7 mg (2.1 μmol, 28%). Analytical data: ^{1}H NMR (acetonitrile-d_3, 400 MHz): δ (ppm) −49.86, −29.61, −12.25, −7.38, −5.95, 1.09, 1.31, 3.67, 8.07, 16.34, 12.88, 13.05, 20.43, 21.75, 36.65, 39.81, 40.01, 40.43, 61.57, 65.94; ESMS: 1575, $Co_4(\mathbf{6a})_4(BF_4)_6^{2+}$.
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