A Simplified Approach to N- and N,N′-Linked 1,2,4-Triazoles by Transamination

Anil D. Naik,[a] Jacqueline Marchand-Brynaert,[b] Yann Garcia*[a]

[a] Unité de Chimie des Matériaux Inorganiques et Organiques, Département de Chimie, Faculté des Sciences, Université Catholique de Louvain, Place L. Pasteur 1, 1348 Louvain-la-Neuve, Belgium

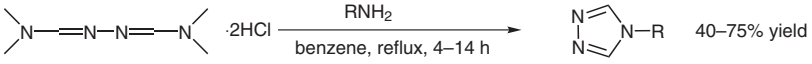
[b] Unité de Chimie Organique et Médicinale, Département de Chimie, Faculté des Sciences, Université Catholique de Louvain, Place L. Pasteur 1, 1348 Louvain-la-Neuve, Belgium
Fax +32(10)472330; E-mail: garcia@chim.ucl.ac.be

Received 15 March 2007; revised 8 June 2007

PSP No 107

Abstract: A facile one-step procedure for the preparation of 4,4′-bis-1,2,4-triazole is reported. Direct transamination of *N,N*-dimethylformamide azine dihydrochloride by heating with 4-amino-1,2,4-triazole in refluxing benzene readily yields the target molecule in short duration of time with significant yield (73%). This catalyst-free method was extended to synthesise a series of 4-substituted 1,2,4-triazoles of potential interest in coordination chemistry.

Key words: amines, amino acids, ligands, transamination, 4,4′-bis-1,2,4-triazole



Scheme 1

4-Substituted 1,2,4-triazoles are important molecules with significant properties that have found widespread applications in foremost sectors of chemical sciences. The anticancer, anticonvulsant, antifungal, anti-inflammatory and antibacterial activities of these molecules are well acknowledged in medicinal and pharmaceutical chemistry.[1] As plant growth regulators,[2] herbicides and pesticides,[3,4] high energy density materials,[5] inhibitors for corrosion and colour photography couplers,[6] they fortify their place in chemical industry. They are also largely used as synthons[7] and ligands in coordination chemistry[8] finding applications as molecular magnetic materials[9,10] and dye-molecules in regenerative solar cells.[11] 4-Substituted 1,2,4-triazoles are also used in supramolecular chemistry as suitable templates for the construction of nanoporous coordination networks.[12]

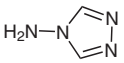
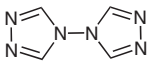
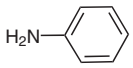
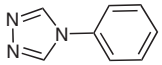
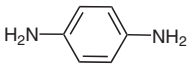
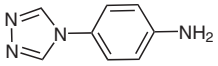
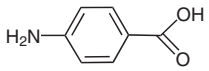
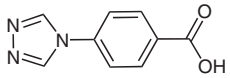
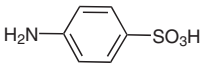
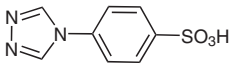
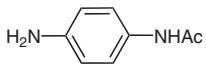
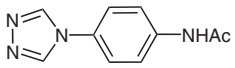
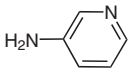
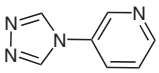
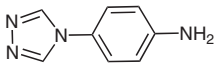
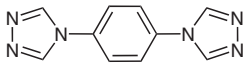
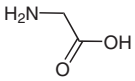
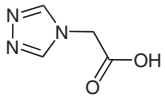
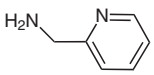
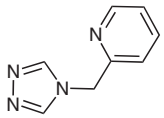
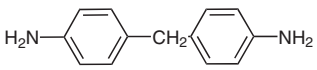
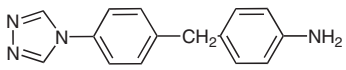
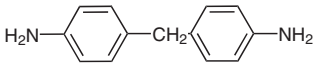
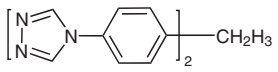
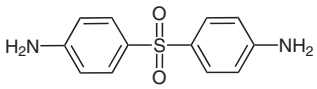
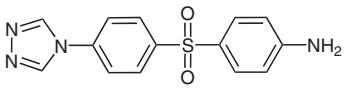
A close literature survey reveals only few reports on the synthesis of asymmetric or symmetric N,N′-linked bis-azoles and *N*-aryl azoles.[13–19] Nowadays, there is a patented procedure of Bayer et al. which is routinely used for producing 4-substituted 1,2,4-triazoles.[3] This procedure involves the addition of a primary amine on the intermediate formed by the reaction of formic acid hydrazide with triethyl orthoformate. This one-pot synthesis affords 4-substituted 1,2,4-triazoles in moderate to good yields depending on the nature of the substituent R.[3,4] This method suffers from the limitation of workup procedure that can involve tedious chromatographic separations particularly when the target triazoles are oils or semi-solids with high molecular weight.[20] In 1967, Bartlett and Humphrey reported a multi-step synthesis of 4,4′-bis-1,2,4-triazole (btr, **4a**) by the transamination of *N,N*-dimethylformamide azine **2** with 4-amino-1,2,4 triazole (NH_2trz, **3a**) in the presence of a catalytic amount of *p*-toluenesulfonic acid in refluxing toluene for 72 hours in appreciable yield (64%) (Scheme 2).[13] The reactive agent (chloromethylene)dimethylammonium chloride $[Me_2N^+{=}CHCl]Cl^-$, which was proposed[19] to be generated from a solution of thionyl chloride in DMF, reacts with hydrazine to produce *N,N*-dimethylformamide azine dihydrochloride **1**. The strategy followed to obtain the free base **2** from **1** is quite monotonous. The dihydrochloride in water was treated with aqueous Na_2CO_3 and the solution continuously extracted with ether for 2 days from which **2** is obtained in 89% yield. Schultze et al. [21] reported a simpler alternative for the above conversion while working on 1,3,4-thiadiazole where the dihydrochloride in EtOH at 0 °C was treated with a NaOEt solution. Subsequent workup gave **2** in 95% yield. Haasnoot and Groeneveld[14] were also credited for their report on the direct approach to the synthesis of **4a** by a one-step reaction between NH_2trz and diformylhydrazine (Scheme 3). Nevertheless, this method suffers from several drawbacks such as low yield (25%), high temperature for the reaction, tedious workup, and uncertainties in reproducibility. Therefore the synthesis of *N,N′*-bis-1,2,4-triazoles that is of high importance in coordination and supramolecular chemistry on account of their multidenticity and ability to be involved in H-bonding,[22] require another procedure. We propose herein an improved synthetic method for **4a** that has been applied to a series of 1,2,4-triazole derivatives **4b–m** (Scheme 1,

SYNTHESIS 2008, No. 1, pp 0149–0154
Advanced online publication: 11.09.2007
DOI: 10.1055/s-2007-983896; Art ID: T05507SS

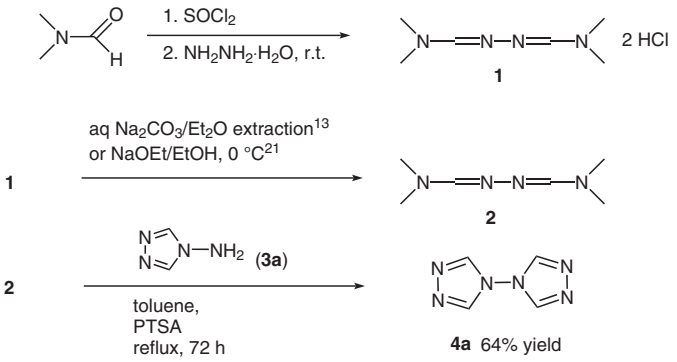
Table 1). Such efficient and rapid synthetic recipes are the demands of commerce, a noteworthy example being a recently documented rapid synthesis of 1*H*-tetrazoles.[28] As illustrated in Table 1, various amines including amino acids turned out to be valuable exchanging partners. The results are compared and discussed with other known synthetic methods for the sake of comparison.

Conventional perception advices the synthesis of **4a** and related molecules[13,16–18] by engaging **2** in the crucial transamination step with amines and acidic catalyst. It is however observed that, particularly in the case of **4a**, the reproducibility in terms of yield and reaction time are often to be faced. Rewardingly, this turns out not to be the case when one starts from **1**, the dihydrochloride of **2**. Bartlett and Humphrey[13] mentioned in their report that transamination step can also be catalysed by **1**, but not as effectively as by *p*-TsOH. Our synthetic approach is conceptually based on this idea. As these amine exchange reactions are generally catalysed by acids,[29] we vision that reactant **1** itself plays that role in the reaction. Yield and duration of time were improved in benzene compared to toluene as the effective azeotropic removal of HCl is facilitated in it, shifting the equilibrium towards the target product.

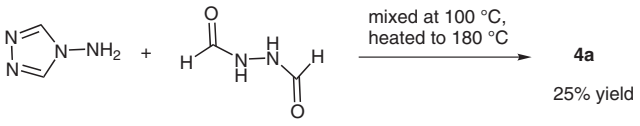
Table 1 Reaction of Various Amines with *N*,*N*-Dimethylformamide Azine Dihydrochloride

Entry	RNH_2	Entry	Product	Reaction time[a] (h)	Reaction time[b] (h)	Yield (%)[a]	Yield (%)[b]
3a		**4a**		12	72	73	64[13]
3b		**4b**		4	3.5[c]	60	78[13]
3c		**4c**		7	1.5[d]	58	76[23]
3d		**4d**		7	–	68	55[3,24]
3e		**4e**		14	–	45	<73[25]
3f		**4f**		8	17	75	91[18]
3g		**4g**		6	0.5	40	42[26]
3h		**4h**		8	–	45	–[27]
3i		**4i**		9	–	50	–
3j		**4j**		8	–	55	–
3k		**4k**		7	–	70	
3l		**4l**		8	–	75	–
3m		**4m**		7	–	74	–

[a] Our method.
[b] Reported method.
[c] With excess of aniline.
[d] Multi-step synthesis.



Scheme 2 Multi-step synthesis of *N*,*N*′-bis-1,2,4-triazole (**4a**)[13]



Scheme 3 One-step route to *N*,*N*′-bis-1,2,4-triazole (**4a**)[14]

It is convenient to note that most of the transamination products (**4a–h**) were reported by other methods, thus allowing a suitable comparison and offering the possibility to test our procedure. In most of the documented cases, our method appears to be superior, being uncomplicated, single-step, and without chromatographic separation for the isolation of the final target molecule. It also shows a better yield, involves shorter reaction time, avoids unnecessary additional step and is cheaper (Table 1). We assume that this transamination reaction should permit the exchange of a larger range of amines, which undoubtedly would widen its synthetic interest as revealed in our amine exchange process. Nevertheless steric factors and the basicity of amines will govern the course of the reaction. The fact that glycine (**3i**), an amino acid was successfully exchanged (to give **4i**) in the amine exchange process is promising to construct an azole moiety on the amino acid backbone which may lead to novel biochemical applications. These molecules could also be used as potential templates in the coordination networks of spin crossover supramolecular assemblies. A preliminary investigation reveals that iron(II) coordination compounds of **4e**,**4j** and **4k** display a colour change from white to pink on cooling, a thermochromic behaviour that can be anticipated to be associated to spin crossover phenomenon. Such inorganic syntheses are in progress in our laboratories.

Procedures

Solvents were dried prior to use. Reagents (Aldrich, Acros, Merck, Lancaster, Avocado Research chemicals or Fischer) were used as received. ^{1}H and ^{13}C NMR spectra were recorded at 250 MHz and 300 MHz on a Bruker AC 250 and Bruker AC 300 instruments, respectively. TMS and sodium 3-(trimethylsilyl)-1-propane sulfonate were used as internal references in $CDCl_3$ and D_2O, respectively. For other solvents the residual solvent peak was used as internal reference. IR spectra were recorded on a Bio-Rad FTS 135 spectrometer using KBr discs. Mass spectral data were obtained on Thermo Finnigan LCQ Ion trap spectrometer (APCI mode). CHN analyses were performed at the University College, London (UK). Melting points were determined with an oil bath 3937-S Büchi device (T ≤ 220 °C) or on a Mettler Toledo analyser DSC 20.

***N*,*N*-Dimethylformamide Azine Dihydrochloride (1)**

$SOCl_2$ (28.6 mL, 0.4 mol) or oxalyl chloride (34.5 mL, 0.4 mol) was added with stirring to freshly distilled DMF (150 mL) at 5 °C. To the aged (24 h) solution of this mixture, was added slowly aqueous hydrazine hydrate (5 mL, 0.1 mol) in DMF (20 mL). The mixture was stirred at r.t. for 2 d and the white precipitate of dimethylformamide azine dihydrochloride was collected by filtration and washed with DMF and Et_2O;[13] yield: 19.4 g (91%); mp 251 °C (Lit.[13] mp 250 °C). (***Caution***: Benzene is potentially *carcinogenic*; all operations involving this solvent should be conducted in a fume hood.)

4,4′-Bis-1,2,4-triazole (4a)

The reaction was carried out in a dry round-bottomed flask fitted with a reflux condenser. To a suspension of **1** (9 g, 0.042 mol, 1 equiv) in benzene (30 mL) was added rapidly solid 4-amino-1,2,4 triazole (**3a**; 4.24 g, 0.05 mol, 1.2 equiv) with stirring. The mixture was gently heated at the beginning until all the suspension had dissolved and reappeared as a white pasty mass. The mixture was refluxed then for 12 h with vigorous stirring. The reaction was monitored by recording ^{1}H NMR spectra of the pasty mass withdrawn at intervals of time. The white precipitate obtained was collected by filtration and washed with cold EtOH (1 × 3 mL) and Et_2O (1 × 5 mL). Recrystallisation from MeOH gave colourless crystals. The spectroscopic data were in accord with the literature value;[13,14] yield: 4.2 g (73%). Small amounts of product can also be obtained by replacing 4-amino-1,2,4 triazole (**3a**) with hydrazine hydrate.

N-Linked 1,2,4-triazoles 4b–m; General Procedure

The following compounds were prepared using a general procedure which is essentially similar to that used for **4a** with variation in reaction time (Table 1), isolation, and purification of products.

4-Phenyl-4*H*-1,2,4-triazole (4b)

A mixture of aniline (**3b**; 0.83 mL, 9.33 mmol, 1 equiv) and **1** (2 g, 9.33 mmol, 1 equiv) was refluxed for 4 h in benzene (20 mL). The white solid that separated was filtered, washed with cold EtOH (1 × 3 mL) followed by Et_2O (1 × 5 mL), and dried under vacuum; yield: 0.780 g (60%); mp 121 °C (Lit.[13] mp 120 °C).

4-(4-Aminophenyl)-4*H*-1,2,4-triazole (4c)

Freshly recrystallised 1,4-phenylenediamine (**3c**; 1.01 g, 9.33 mmol, 1 equiv) and **1** (2 g, 9.33 mmol, 1 equiv) were mixed and refluxed in benzene (20 mL) for 7 h with vigorous stirring. The residue obtained after evaporating benzene was dissolved in EtOH (6 mL) and filtered off from the insoluble solid. The filtrate was concentrated to obtain a white solid, which was filtered, washed with

cold EtOH (1 × 1 mL), and dried under vacuum; yield: 0.863 g (58%); mp 195 °C.

IR (KBr): 3109 (m), 1540 (s), 1501 (s), 1315 (m), 1240 (m), 1012 (m), 862 (s), 636 (m), 509 cm^{-1} (s).

^1H NMR (250 MHz, DMSO-d_6, 298 K): δ = 8.86 (s, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 6.68 (d, *J* = 8.7 Hz, 2 H), 5.44 (br, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6, 298 K): δ = 141.4, 134, 133.3, 131.6, 122.6.

4-(4*H*-1,2,4-Triazol-4-yl)benzoic Acid (4d)

Refluxing a mixture of **1** (2g, 9.33 mmol, 1 equiv) and 4-aminobenzoic acid (**3d**; 1.28 g, 9.33 mmol, 1 equiv) in benzene (25 mL) for 7 h gave a pale yellow solid, which was filtered and washed with EtOH (1 × 3 mL) and Et_2O (1 × 5 mL); yield: 1.19 g (68%); mp 334 °C.

IR (KBr): 3423 (br), 3112 (m), 1687 (s), 1608 (s), 1533 (s), 1452 (m), 1319 (s), 1085 (s), 1014 (s), 860 (s), 769 (s), 622 cm^{-1} (m).

^1H NMR (250 MHz, DMSO-d_6, 298 K): δ = 9.27 (s, 2 H), 8.11 (d, *J* = 8.7 Hz, 2 H), 7.85 (d, *J* = 8.7 Hz, 2 H).

^{13}C NMR (62.5 MHz, DMSO-d_6, 298 K): δ = 166.4, 141.3, 132.6, 131.2, 130.1, 121.

4-(4*H*-1,2,4-Triazol-4-yl)benzenesulfonic Acid (4e)

Azine **1** (2 g, 9.33 mmol, 1 equiv) was suspended in benzene (30 mL) and heated slowly to 60 °C. Sulfonic acid **3e** (1.61 g, 9.33 mmol, 1 equiv) was added to the above solution and the mixture was vigorously stirred and refluxed for 14 h. The creamy solid obtained was washed with H_2O (1 × 3 mL) to remove the unreacted sulfonic acid **3e**, followed by EtOH (1 × 3 mL) and Et_2O (1 × 4 mL); yield: 0.94 g (45%); mp >398 °C.

IR (KBr): 3114 (m), 1596 (m), 1564 (s), 1423 (m), 1367 (m), 1201 (m), 1112 (m), 1035 (s), 1014 (s), 946 (m), 842 (m), 754 (m), 634 (s), 567 cm^{-1} (s).

^1H NMR (250 MHz, DMSO-d_6, 298 K): δ = 9.65 (s, 2 H), 7.68–7.8 (ABq, *J* = 8.7 Hz, 4 H).

^{13}C NMR (62.5 MHz, DMSO-d_6): δ = 163.1, 141.9, 131.7, 127.2, 121.3.

***N*-(4-(4*H*-1,2,4-Triazol-4-yl)phenyl)acetamide (4f)**

Refluxing a mixture of **1** (2 g, 9.33 mmol, 1 equiv) and 4′-aminoacetanilide (**3f**; 1.4 g, 9.33 mmol, 1 equiv) in benzene (25 mL) for 8 h afforded a beige solid, which was washed with EtOH (1 × 3 mL) and dried; yield: 1.4 g (75%); mp 289 °C.

^1H NMR (250 MHz, DMSO-d_6, 298 K): δ = 10.18 (s, 1 H, NH), 9.04 (s, 2 H), 7.75 (d, *J* = 8.7 Hz, 2 H), 7.59 (d, *J* = 8.7 Hz, 2 H), 2.07 (s, 3 H).[18]

4-(Pyridin-3-yl)-4*H*-1,2,4-triazole (4g)

A mixture of **1** (2 g, 9.3 mmol, 1 equiv) and 3-aminopyridine (**3g**; 0.878 g, 9.3 mmol, 1 equiv) were mixed and refluxed for 6 h in benzene (25 mL). The turbid solution was cooled to r.t. and the white solid separated was filtered and suspended in a small amount of cold EtOH (1 mL) for a short time, filtered, and dried; yield: 0.54 g (40%); mp 158 °C.

IR (KBr): 1629 (s), 1483 (m), 1430 (m), 1377 (m), 1328 (m), 1251 (m), 1097 (s), 958 (m), 883 (m), 802 (m), 729 (w), 696 cm^{-1} (w).

^1H NMR (250 MHz, $CDCl_3$, 298 K): δ = 8.73–8.68 (m, 2 H), 8.5 (s, 2 H), 7.77–7.82 (m,1 H), 7.47–7.52 (m, 1 H).

^{13}C NMR (62.5 MHz, $CDCl_3$, 298 K): δ = 153.3, 150.4, 143.4, 141.3, 130.0, 124.8.

1,4-Bis(4*H*-1,2,4-triazol-4-yl)benzene (4h)

The compound was prepared from **1** (0.668 g, 3.1 mmol, 1 equiv) and **3h** (≡ **4c**) (0.5 g, 3.1 mmol, 1 equiv) in refluxing benzene (25 mL) for 8 h, as a white solid, but it can also be prepared from **1** and *p*-phenylenediamine in a 2:1 stoichiometric ratio; yield: 0.28 g (45%); mp 320 °C.

IR (KBr): 3108 (m), 3016 (m), 1540 (s), 1508 (s), 1315 (m), 1240 (m), 1089 (m), 1037 (m), 1014 (m), 862 (s), 636 cm^{-1} (m).

^1H NMR (250 MHz, DMSO-d_6, 298 K): δ = 9.22 (s, 4 H), 7.95 (s, 4 H).

^{13}C NMR (62.5 MHz, DMSO-d_6, 298 K): δ = 141.3, 122.6, 121.

4-(4*H*-1,2,4-Triazol-4-yl)acetic Acid (4i)

Azine **1** (2 g, 9.33 mmol, 1 equiv) was suspended in benzene (30 mL) and warmed slowly to around 55–60 °C. Glycine (**3i**; 0.7 g, 9.33 mmol, 1 equiv) was added to this solution. The resulting mixture was stirred at this temperature until all the suspension had dissolved and reappeared as pale yellow oil that was then refluxed for 8–9 h. The oily residue obtained after removing benzene under reduced pressure was dissolved in EtOH (2 mL) and filtered off from unreacted glycine. EtOH was then removed under reduced pressure and the colourless oil was cooled in ice to obtain white crystals; yield: 0.59 g (50%); mp 161 °C. (***Caution***: Fluctuation in temperature and ineffective stirring often gave a white solid, which was probably **4i** with bonded hydrochloride of glycine.)

IR (KBr): 3442 (br), 3110 (s), 1900 (s), 1548 (m), 1496 (m), 1257 (s), 1191 (m), 1087 (m), 1020 (s), 970 (s), 883 (s), 790 (s), 655 (s), 622 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6, 298 K): δ = 8.49 (s, 2 H), 4.98 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6, 298 K): δ = 170.1, 144.8, 46.3.

MS: *m*/*z* = 128.04 ($M + H^+$).

Anal. Calcd for $C_4H_5N_3O_2$ (127.10): C, 37.80; H, 3.97; N, 33.06. Found: C, 37.57, H, 4.10, N, 32.59.

4-(Pyridin-2-yl-methyl)-4*H*-1,2,4-triazole (4j)

A mixture of **1** (2 g, 9.33 mmol, 1 equiv) and 2-(aminomethylpyridine) (**3j**; 0.96 mL, 9.33 mmol, 1 equiv) in benzene (20 mL) was refluxed for 8 h. The oily residue obtained after removing benzene under reduced pressure was dissolved in EtOH (2 mL) and the compound was precipitated by dropwise addition of Et_2O. The white solid, which usually turned to pale yellow upon keeping in air, was collected and dried under vacuum (hygroscopic); yield: 0.818 g (55%); mp 77–80 °C.

IR (KBr): 1646 (m), 1637 (m), 1592 (s), 1571 (m), 1529 (s), 1479 (m), 1434 (s), 1187 (s), 1076 (s), 997 (m), 871 (m), 752 (s), 700 (m), 647 cm^{-1} (s).

^1H NMR (250 MHz, $CDCl_3$, 298 K): δ = 8.54–8.56 (m, 1 H), 8.28 (s, 2 H), 7.64–7.71 (m, 1 H), 7.22–7.27 (m, 1 H), 7.13 (d, *J* = 8 Hz, 1 H), 5.27 (s, 2 H).

^{13}C NMR (62.5 MHz, $CDCl_3$, 298 K): δ = 154, 150.2, 143.2, 137.6, 123.7, 121.9, 50.6.

MS: *m*/*z* = 161.22 ($M + H^+$).

Anal. Calcd for $C_8H_8N_4$ (160.18): C, 59.99; H, 5.03; N, 34.98. Found: C, 58.10; H, 4.92; N, 33.27.

4-{4-[(4-Aminophenyl)methyl]phenyl}-4*H*-1,2,4-triazole (4k)

4,4′-Diaminodiphenylmethane (**3k**; 1.85 g, 9.33 mmol, 1 equiv) was suspended in benzene (40 mL) and warmed to 60 °C. To this solution was added slowly a solution of **1** (2 g, 9.33 mmol, 1 equiv) in benzene (20 mL) with vigorous stirring. The pale yellow pasty mass obtained was refluxed for 7 h. The solid lumps obtained were

filtered, dried, and washed with cold EtOH (2 mL). It was then dissolved in MeOH (10 mL) and layered with Et_2O (5 mL). Pale yellow crystals thus obtained were filtered and dried; yield: 1.62 g (70%); mp 222 °C.

IR (KBr): 3348 (m), 3197 (m), 3087 (m), 1633 (s), 1616 (s), 1296 (m), 1091 (s), 1000 (s), 811 (s), 653 cm^{-1} (m).

^1H NMR (300 MHz, DMSO-d_6, 298 K): δ = 9.08 (s, 2 H), 7.61 (d, *J* = 8.5 Hz, 2 H), 7.38 (d, *J* = 8.5 Hz, 2 H), 6.91 (d, *J* = 8.3 Hz, 2 H), 6.52 (d, *J* = 8.3 Hz, 2 H), 4.92 (br, 2 H), 3.84 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6, 298 K): δ = 147.6, 143.4, 142.1, 132.5, 130.6, 129.9, 128.5, 122, 114.8, 38.2.

MS: *m*/*z* = 251.70 ($M + H^+$).

Anal. Calcd for $C_{15}H_{14}N_4$ (250.30): C, 71.98; H, 5.64; N, 22.38. Found: C, 72.14; H, 5.95; N, 22.48.

Bis[4-(4*H*-1,2,4-triazol-4-yl)phenyl]methane (4l)

The pasty mass obtained after mixing 4,4′-diaminodiphenylmethane [**3l** (≡ **3k**) 0.925 g, 4.66 mmol, 1 equiv] and **1** (2 g, 9.33 mmol, 2 equiv) in benzene (25 mL) was stirred vigorously and refluxed for 8 h. The pale yellow solid obtained was filtered, and washed with cold EtOH (1 × 3 mL). The solid was dissolved in hot EtOH (10 mL), treated with a pinch of charcoal and filtered. White crystals obtained was separated and dried under vacuum; yield: 2.10 g (75%); mp 262 °C.

IR (KBr): 3095 (m), 2775 (m), 1635 (m), 1562 (m), 1523 (s), 1243 (s), 1095 (s), 998 (m), 867 (m), 817 (m), 792 (s), 636 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6, 298 K): δ = 9.1 (s, 4 H), 7.65 (d, *J* = 8.5 Hz, 4 H), 7.45 (d, *J* = 8.5 Hz, 4 H), 4.0 (s, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6, 298 K): δ = 141.6, 133, 132, 130.2, 121.8, 34.8.

MS: *m*/*z* = 303.04 ($M + H^+$).

Anal. Calcd for $C_{17}H_{14}N_6$ (302.34): C, 67.54; H, 4.67; N, 27.80. Found: C, 67.79, H, 5.03, N, 27.36.

4-{4-[(4-Aminophenyl)sulfonyl]phenyl}-4*H*-1,2,4-triazole (4m)

To a warmed suspension of **1** (2 g, 9.33 mmol, 1 equiv) in benzene (35 mL) was added slowly a solution of 4,4′-diaminodiphenyl sulfone (**3m**; 2.317 g, 9.33 mmol, 1 equiv) in benzene (15 mL). Within 15–20 min a pale yellow semisolid appeared. The mixture was refluxed with vigorous stirring for 7 h. The solid was filtered and washed with EtOH (3 mL). Recrystallisation from hot MeOH gave white crystals; yield: 2.06 g (74%); mp 254 °C.

IR (KBr): 3411 (br), 3323 (m), 3203 (m), 3134 (m), 1629 (m), 1590 (s), 1525 (s), 1504 (m), 1301 (s), 1150 (s), 1107 (s), 673 (s), 595 (s), 555 cm^{-1} (s).

^1H NMR (300 MHz, DMSO-d_6, 298 K): δ = 9.22 (s, 2 H), 8.03 (d, *J* = 8.8 Hz, 2 H), 7.93 (d, *J* = 8.8 Hz, 2 H) 7.62 (d, *J* = 8.8 Hz, 2 H), 6.65 (d, *J* = 8.8 Hz, 2 H), 6.25 (br, 2 H).

^{13}C NMR (75 MHz, DMSO-d_6, 298 K): δ = 154.7, 143.3, 142.1, 137.7, 130.4, 129.2, 125.6, 122.8, 113.9.

MS: *m*/*z* = 301.18 ($M + H^+$).

Anal. Calcd for $C_{14}H_{12}N_4O_2S$ (300.34): C, 55.99; H, 4.03; N, 18.65. Found: C, 55.40; H, 4.79; N, 17.46.

Acknowledgment

We gratefully acknowledge the financial support from the *Fonds Special de Recherche* of the Université Catholique de Louvain and the IAP-VI (P6/17) programme. J. Marchand-Brynaert is a senior research associate of the FNRS (Belgium).

References

(1) (a) Kane, J. M.; Baron, B. M.; Dudley, M. W.; Soressen, S. M.; Staeger, M. A.; Miller, F. P. *J. Med. Chem.* **1990**, *33*, 2772. (b) Menegola, E.; Broccia, M. L.; Di Renzo, F.; Giavini, E. *Reprod. Toxicol.* **2006**, *22*, 186. (c) Chollet, J. F.; Bonnemain, J. L.; Miginiac, L.; Rohr, O. *J. Pestic. Sci.* **1990**, *29*, 427. (d) Holla, B. S.; Veerendra, B.; Shivananda, M. K.; Poojary, B. *Eur. J. Med. Chem.* **2003**, *38*, 759.

(2) Meister, R. T. *Chemical Handbooks '92*; Meister Publishing Company: Willoughby OH / USA, **1992**, .

(3) Bayer, H. O.; Cook, R. S.; von Meyer, W. C. US Patent 382137628, **1974**; *Chem. Abstr.* **1972**, *76*, 113224.

(4) Seidel, L.; von Meyer, W. C.; Greenfield, S. US Patent 4120684, **1978**; *Chem. Abstr.***1979**, *90*, 54948.

(5) Sivabalan, R.; Anniyappan, M.; Pawar, S. J.; Talawar, M. B.; Gore, G. M.; Venugopalan, S.; Gandhe, B. R. *J. Hazard. Mater.* **2006**, *137*, 672.

(6) (a) Bentiss, F.; Bouanis, M.; Mernari, B.; Traisnel, M.; Vezin, H.; Lagrenee, M. *Appl. Surf. Sci.* **2007**, *235*, 3696. (b) House, G. L.; Levy, D. H.; Yang, X.; Slusarek, W. *J. Imaging Sci. Technol.* **2005**, *49*, 398.

(7) Laus, G.; Kloetzer, W. *Synthesis* **1989**, 269.

(8) (a) Haasnoot, J. G. In *Magnetism: A Supramolecular Function*; Kahn, O., Ed.; Kluwer Academic Publishers: Dordrecht, **1996**, 299. (b) Haasnoot, J. G. *Coord. Chem. Rev.* **2000**, *200/202*, 131.

(9) Garcia, Y.; Niel, V.; Muñoz, M. C.; Real, J. A. *Top. Curr. Chem.* **2004**, *233*, 229.

(10) Ouellette, W.; Galán-Mascarós, J. R.; Dunbar, K. R.; Zubieta, J. *Inorg. Chem.* **2006**, *45*, 1909.

(11) Lees, A. C.; Evrard, B.; Keyes, T. E.; Vos, J. G.; Kleverlaan, C. J.; Alebbi, M.; Bignozzi, C. A. *Eur. J. Inorg. Chem.* **1999**, 2309.

(12) Zhang, J.-P.; Lin, Y. Y.; Zhang, W.-X.; Chen, X.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14162.

(13) Bartlett, R. K.; Humphrey, I. R. *J. Chem. Soc. C* **1967**, 1664.

(14) Haasnoot, J. G.; Groeneveld, W. L. *Z. Naturforsch., B: Anorg. Chem. Org. Chem.* **1979**, *34*, 1500.

(15) Katritzky, A. R.; Suwinski, J. W. *Tetrahedron* **1975**, *31*, 1549.

(16) (a) de Mendoza, J.; Castellanos, M. L.; Fayet, J.-P.; Vertut, M. C.; Elguero, J. *J. Chem. Res., Synop.* **1980**, 50. (b) Curtis, A. D. M. In *Science of Synthesis*, Vol. 13; Storr, R.; Gilchrist, T., Eds.; Thieme: Stuttgart, **2004**, 603.

(17) (a) Castellanos, M. L.; Llinas, M.; Bruix, M.; de Mendoza, J.; Martin, M. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1209. (b) Woisel, P.; Cazier, F.; Surpateanua, G.; Baudel, V.; Boursier, V. *Heterocycl. Commun.* **2002**, *8*, 71.

(18) (a) Sternfeld, F.; Guiblin, A. R.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Hunt, P. A.; Beer, M. S.; Held, A.; Stanton, J. A.; Sohal, B.; Watt, A. P.; Street, L. J. *J. Med. Chem.* **1999**, *42*, 677. (b) Bouchet, P.; Coquelet, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 449.

(19) Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653.

(20) (a) Boland, Y.; Attout, A.; Marchand-Bryanert, J.; Garcia, Y. *J. Chromatogr., A* **2007**, *1141*, 145. (b) Boland, Y.; Hertsens, P.; Marchand-Bryanert, J.; Garcia, Y. *Synthesis* **2006**, 1504.

(21) Fohlisch, B.; Braun, R.; Schultze, K. W. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 361.

(22) (a) Garcia, Y.; Kahn, O.; Rabardel, L.; Chansou, B.; Tuchagues, J.-P. *Inorg. Chem.* **1999**, *38*, 4663. (b) Garcia, Y.; van Koningsbruggen, P. J.; Kooijman, H.; Spek, A. L.; Haasnoot, J. G.; Kahn, O. *Eur. J. Inorg. Chem.* **2000**, 307. (c) Garcia, Y.; van Koningsbruggen, P. J.; Kooijman, H.; Spek, A. L.; Haasnoot, J. G.; Kahn, O. *Eur. J. Inorg. Chem.*

2000, 575.
(23) Sternfeld, F.; Baker, R.; Broughton, H. B.; Guiblin, A. R.; Jelley, R. A.; Matassa, V. G.; Reeve, A. J.; Beer, M. S.; Stanton, J. A.; Hargreaves, R. J.; Shepheard, S. L.; Longmore, J.; Razzaque, Z.; Graham, M. I.; Sohal, B.; Street, L. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1825.
(24) Zou, R.-Q.; Cai, L.-Z.; Guo, G.-C. *J. Mol. Struct.* **2005**, *737*, 125.
(25) Mozolis, V.; Rastenyte, L.; Gurkliene, M. *Chemija* **1987**, *4*, 50; *Chem. Abstr.* **1998**, *109*, 6465.
(26) Wiley, R. H.; Hart, A. J. *J. Org. Chem.* **1953**, *18*, 1368.
(27) Cai, H.; Hu, H.-M.; Chen, W.-Z.; Xu, Y.; You, X.-Z. *Acta Crystallogr., C: Cryst. Struct. Commun.* **1999**, *55*, IUC9900082.
(28) (a) Potewar, T. M.; Siddiqui, S. A.; Lahoti, R. J.; Srinivasan, K. V. *Tetrahedron Lett.* **2007**, *48*, 1721. (b) Siddiqui, S. A.; Potewar, T. M.; Lahoti, R. J.; Srinivasan, K. V. *Synthesis* **2006**, 2849. (c) Siddiqui, S. A. *Synlett* **2006**, 155.
(29) Martin, J. C.; Barton, K. R.; Gott, P. G.; Mean, R. H. *J. Org. Chem.* **1966**, *31*, 943.