Azoles. Part 13.[1,2] Synthesis and bromine ⟶ lithium exchange reactions of some 1-substituted 4,5-dibromo-1*H*-1,2,3-triazoles and 2-substituted 4,5-dibromo-2*H*-1,2,3-triazoles

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4,5-Dibromo-1*H*-1,2,3-triazole was synthesised by various routes and reacted with chloromethyl methyl ether (N-1/2), methyl chloroformate (N-1), benzyl chloride (N-1), 4-methoxybenzyl chloride (N-1), 4-nitrobenzyl chloride (N-1/2) or triphenylmethyl chloride (N-2) under various conditions, to give isolable products substituted at the N-atoms shown in parentheses.

4,5-Dibromo-1-methoxymethyl-1*H*- and -2-methoxymethyl-2*H*-1,2,3-triazole reacted with butyllithium (in diethyl ether or tetrahydrofuran at low temperatures) at position-5 and the resulting lithiated derivatives were quenched with aqueous ammonium chloride, carbon dioxide, methyl chloroformate, benzophenone or dimethyl or diphenyl disulfide to give high yields (71–93%) of the corresponding 5-substituted 1,2,3-triazole. 1-Benzyl-4,5-dibromo-1*H*-1,2,3-triazole was converted similarly into 1-benzyl-4-bromo-5-methylsulfanyl-1*H*-1,2,3-triazole (91.5%). In a 'one pot' sequence and through two successive treatments with butyllithium and the appropriate quenching reagent (Ph_2S_2 and H_2O), 4,5-dibromo-2-methoxymethyl-2*H*-1,2,3-triazole was converted similarly into 2-methoxymethyl-4-phenylsulfanyl-2*H*-1,2,3-triazole (47% yield).

As far as we are aware there are no previous literature reports on the synthesis of 1,2,3-triazoles *via* Br ⟶ Li exchange reactions (apart from the preliminary reports on this work[2]),[2a,3–6] although the chlorine atom in 5-chloro-1,4-diphenyl-1*H*-1,2,3-triazole is reported[7] to be reactive enough to undergo Cl ⟶ Li exchange with butyllithium.

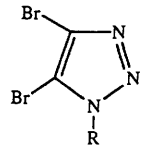
1-Protected 1*H*-1,2,3-triazoles [protecting group = $CMe(OEt)_2$,[8] $CH_2OCH_2CH_2SiMe_3$ (SEM),[9] CH_2Ph,[10–12] or Ph[7,10,13]] are metallated in position-5 and, providing the temperature is kept low, the resulting 5-lithiated derivatives can be quenched with a suitable electrophile.[2a] An attempt to metallate 2-SEM-protected 2*H*-1,2,3-triazole failed[9] whilst metallation of a mixture of 1-diethoxyethyl-1*H*- and 2-diethoxyethyl-2*H*-1,2,3-triazole with butyllithium followed by a 4,4′-dichlorobenzophenone quench gave a very low yield (17%) of the N-deprotected quenched product.[8]

Metallation of 1-phenyl-1*H*-1,2,3-triazole[13] and some of its 4-substituted derivatives (substituent = Me,[13] Ph,[7,10,13] $CONEt_2$[10] or 4,5-dihydro-4,4-dimethyloxazol-2-yl[10]) results in the formation of a 5-lithiated derivative, which fragments if the temperature is allowed to rise, with release of nitrogen and formation of ions with the general structure Ph–NLi–C≡C–R. If position-5 is blocked, as in 1,5-diphenyl-1*H*-1,2,3-triazole, then the 4-lithiated derivative is formed.[13]

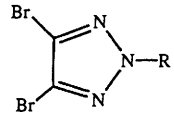
In continuation of our studies[1,2] on lithiated azoles we now report on the synthesis of some 1-substituted 4,5-dibromo-1*H*- (**1**–**5**) and 2-substituted 4,5-dibromo-2*H*-1,2,3-triazoles (**6**–**9**) and on the Br ⟶ Li exchange reactions of compounds **1**, **4** and **7**. Begtrup and co-workers have synthesised polyfunctionalised 1,2,3-triazoles *via* the synthesis and deprotonation of various 1,2,3-triazole 1-oxides and related compounds.[14–18]

Two approaches for the synthesis of our starting materials were considered: (i) N-alkylation of the known 4,5-dibromo-1,2,3-triazole; and (ii) bromination of known 1-substituted 1*H*-1,2,3-triazoles.[5]

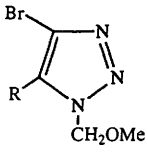
The parent heterocycle, which undergoes elemental bromination to give its 4,5-dibromo derivative,[5,19,20] is available commercially but is prohibitively expensive. The most direct route for its synthesis involves addition of hydrazoic acid to acetylene under pressure.[5,21] However, because this route is not



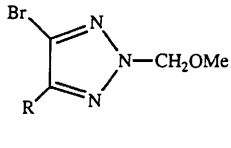
1 R = CH_2Ph
2 R = $CH_2C_6H_4OMe$-4
3 R = $CH_2C_6H_4NO_2$-4
4 R = CH_2OMe
5 R = CO_2Me



6 R = $CH_2C_6H_4NO_2$-4
7 R = CH_2OMe
8 R = CPh_3
9 R = CH_2OH



10 R = H (84%)
11 R = CO_2H (71.5%)
12 R = $C(OH)Ph_2$ (93%)
13 R = SMe (86.5%)
14 R = SPh (71%)
15 R = CHO (~5%)



16 R = H (91%)
17 R = CO_2Me (71%)
18 R = $C(OH)Ph_2$ (77%)
19 R = SMe (76%)
20 R = SPh (75%)
21 R = CHO (~5%)
22 R = MgBr

'user friendly', we chose instead to synthesise 1*H*-1,2,3-triazole-4-carboxylic acid (70% yield) *via* addition of hydrazoic acid to propiolic acid[5,22–24] and convert it into 4,5-dibromo-1,2,3-triazole by bromodecarboxylation (90–95% yield).[5,19]

We also synthesised 1-benzyl-1*H*-1,2,3-triazole-4,5-dicarboxylic acid (96% yield) *via* addition of benzyl azide to acetylenedicarboxylic acid and converted it into 1-benzyl-1*H*-1,2,3-triazole (94%) through its thermal decarboxylation under reduced pressure.[25] Removal of the benzyl group was

accomplished with hydrogen and 10% palladium–charcoal in dioxane, to give the parent heterocycle in 74% yield.[25]

We have modified this approach to provide a more 'user friendly' route to the parent heterocycle. Thus, 4-methoxybenzyl azide underwent a cycloaddition reaction with acetylenedicarboxylic acid to give 1-(4-methoxybenzyl)-1*H*-1,2,3-triazole-4,5-dicarboxylic acid (84% yield). This was decarboxylated by heating it *in vacuo* and the 1-(4-methoxybenzyl)-1*H*-1,2,3-triazole[26] obtained (95% crude yield) was deprotected by heating it in trifluoroacetic acid in the presence of anisole, to give 1,2,3-triazole in high yield. This route avoids the costly and difficult catalytic debenzylation involved in the preceding route.

Elemental bromination of 1,2,3-triazole afforded 4,5-dibromo-1,2,3-triazole (97% yield).[19,20]

Whilst 2-methyl-2*H*-1,2,3-triazole can be converted into its 4,5-dibromo derivative with elemental bromine, its 1-methyl-1*H*-isomer yields only the 4-monobromo derivative under the same conditions.[5,16,20,24] Likewise, 1-benzyl-1*H*-1,2,3-triazole is reported[27] to give only its 4-monobromo derivative in low yield (33%). Nevertheless we attempted to dibrominate 1-benzyl-1*H*-1,2,3-triazole with an excess of elemental bromine under various conditions (Br_2–CCl_4–ambient temperature or under reflux in the dark; Br_2–CCl_4–Fe powder–ambient temperature or under reflux in the dark; Br_2–AcOH–ambient temperature or under reflux in the dark; Br_2–10% aq. NaOH–under reflux) but we could not detect any of the 4,5-dibrominated compound **1** [by thin layer chromatography (TLC)] in any of the crude products and this route to our starting materials was abandoned.

1,2,3-Triazole alkylates with various substrates (*e.g.* with diazomethane[5,16,22,24] or dimethyl sulfate[5,20]) to give a mixture of the 1-1*H*- and 2-2*H*-alkylated derivatives[5,26,28,29] usually (but not always) with the former predominating. We made several attempts to *N*-benzylate 4,5-dibromo-1,2,3-triazole (*cf.* ref. 26), using benzyl bromide, chloride or iodide with sodium methoxide in methanol or triethylamine in dichloromethane (DCM) at ambient temperature (which gave the best results with benzyl chloride), but isolated only 1-benzyl-4,5-dibromo-1*H*-1,2,3-triazole **1** in low yields (25–30%) and none of the 2-benzyl-2*H*-isomer. By varying temperature (−35 °C to reflux), time of reaction (30 min to 5 days), solvent (CH_2Cl_2, MeOH or Me_2CO) or base (NaOMe, KOBu^t, Et_3N, KOH, $NaHCO_3$, Na_2CO_3, K_2CO_3) no increase in yield could be obtained; in the absence of a base only starting material was recovered. We concluded that the absence of any 2-benzyl-4,5-dibromo-2*H*-1,2,3-triazole in any of our crude products could be attributable to its instability.

Three parallel reactions with benzyl chloride, 4-methoxybenzyl chloride (*cf.* ref. 26) or 4-nitrobenzyl chloride (10.0 mmol) [carried out in DCM (50 cm^3) in the presence of Et_3N (11.0 mmol)] gave, after work-up, 1-benzyl-4,5-dibromo-1*H*-1,2,3-triazole **1** (32% yield), 4,5-dibromo-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole **2**[26] (22%) and a mixture of 4,5-dibromo-1-(4-nitrobenzyl)-1*H*-1,2,3-triazole **3** (29%) and 4,5-dibromo-2-(4-nitrobenzyl)-2*H*-1,2,3-triazole **6** (26%), respectively. An electron-withdrawing substituent appears to stabilise a 2-aryl-substituted 2*H*-1,2,3-triazole.

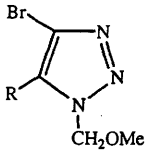
Not surprisingly[29] 4,5-dibromo-1,2,3-triazole reacted with triphenylmethyl chloride (Et_3N in benzene) to give only 4,5-dibromo-2-triphenylmethyl-2*H*-1,2,3-triazole **8** (91% yield). With chloromethyl methyl ether it gave a separable mixture (84%) of 1-methoxymethyl-1*H*- **4** and 2-methoxymethyl-2*H*-1,2,3-triazole **7** (ratio 55:45). Each of these isomers was stable when stored pure (after chromatographic separation on silica) but, when the freshly isolated crude pale yellow product containing both isomers was stored at ambient temperature in daylight for 3 months, large white crystals separated. Initially we concluded that one of the methoxymethyl isomers, **4** or **7**, was crystallising out. However, when these crystals were filtered off, recrystallised and a ^{1}H NMR spectrum recorded a doublet at δ 5.60 typical for a methylene group was observed but no signal characteristic of a methoxy group could be found. A triplet at δ 7.42 was shown to be exchangeable with deuterium oxide, which suggested the presence of a hydroxy group. The IR spectrum of this product confirmed the presence of a hydroxy group (ν_{max}/cm^{-1} 3360). A singlet at δ 124.69 in the ^{13}C NMR spectrum of this compound suggested that it was a 2-substituted 2*H*-1,2,3-triazole; a triplet at δ 77.71 supported the presence of the methylene group. Together with the mass spectral data (molecular ion at *m/z* 255) and microanalytical data this evidence led us to conclude that cleavage of 4,5-dibromo-2-methoxymethyl-2*H*-1,2,3-triazole **7** had occurred, to give the 2-hydroxymethyl compound **9**. Compounds **4**, **7** and **9** were shown by TLC analysis to be present in the stored sample and chromatographic separation on silica provided more of the hydroxymethyl compound **9** together with the two methoxymethyl isomers **4** and **7**. However, the quantity of 4,5-dibromo-1-methoxymethyl-1*H*-1,2,3-triazole **4** isolated was diminished significantly, which suggested that the methoxymethyl group might have undergone a N-1 ⟶ N-2 rearrangement during storage of the mixture. Such rearrangements are not without precedent[5,16,30] and are assisted by the presence of electron-withdrawing substituents elsewhere in the molecule.

A mixture of 4,5-dibromo-1-methoxymethyl-1*H*- and -2-methoxymethyl-2*H*-1,2,3-triazole, **4** and **7**, could be produced and separated readily by chromatography. Therefore, we decided to study their Br ⟶ Li exchange reactions first. Each compound metallated (Et_2O, −70 to −80 °C) at position-5 and the resulting 1,2,3-triazolyllithium compound was quenched with aqueous ammonium chloride, carbon dioxide, methyl chloroformate, benzophenone or dimethyl or diphenyl disulfide at this temperature, to give compounds **10**–**14** and **16**–**20**, respectively in 71–93% yields (see Tables 1 and 2). By quenching either lithium compound with *N*,*N*-dimethylformamide (DMF) or *N*-formylpiperidine at −70 to −80 °C, then allowing the mixtures to warm up to ambient temperature, complex mixtures of products were obtained from which very little (< 5%) of the aldehydes **15** or **21** could be isolated. Likewise, 1-benzyl-4,5-dibromo-1*H*-1,2,3-triazole **1** reacted successively with butyllithium (Et_2O, −70 to −80 °C) and dimethyl disulfide, to give a high yield (91.5%) of the methylsulfanyl derivative **23**, but attempts to prepare the corresponding 5-carbaldehyde failed. Previous attempts to quench 1,2,3-triazolyllithium compounds with DMF have failed.[9] Presumably the temperature at which the formylation reaction begins with those lithiated triazoles is one above which ring-opening reactions occur.

^{13}C NMR spectroscopy readily differentiates between a 2-substituted 4,5-dibromo-2*H*-1,2,3-triazole, which displays only one signal for the ring C-atoms, and its 1-substituted isomer, which displays two distinct signals. For 4,5-dibromo-2-methoxymethyl-2*H*-1,2,3-triazole **7** the Br atoms are identical and, consequently, the structures of products **16**–**20** are unambiguous. The effect of the new substituent on the δ_C value for C-5 can be obtained from these spectra. By using these substituent effects and by comparing the ^{13}C NMR spectra of 4,5-dibromo-1-methoxymethyl-1*H*-1,2,3-triazole **4** with those of the products obtained from its Br ⟶ Li exchange reactions structures **10**–**14** are confirmed. Similar observations can be applied to the determination of the structures of other 1,2,3-triazoles, *e.g.* compounds **1** and **23**. Buckle *et al.*[29] have used ^{1}H and ^{13}C NMR spectroscopy to differentiate between N-1, N-2 and N-3 alkylated 1,2,3-triazoles. In line with their observations the C-atom signals in the ^{13}C NMR spectra of the 1- and 2-methoxymethyl isomers **4** and **7** appear at δ 79.58 and 84.74, respectively.

Both bromine atoms in 4,5-dibromo-2-methoxymethyl-2*H*-1,2,3-triazole **7** may be replaced in a 'one pot' procedure. Thus, *e.g.*, the 5-phenylsulfanyl compound **20** can be prepared, as described in the preceding paragraph, then without isolation it can be reacted with further equivalent of butyllithium and the

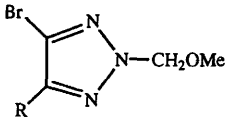
Table 1 4,5-Disubstituted 1-methoxymethyl-1*H*-1,2,3-triazoles



Compound	R	Yield (%)	Mp[a] or bp (*T*/°C, mmHg)	Reagent	Found (%) C	H	N	M^+	Formula	Required (%) C	H	N	δ_H(assignment)[b]
10	H	84	96–101 at 1.5	H_2O	25.4	3.1	21.8		$C_4H_6BrN_3O$	25.0	3.15	21.9	3.37 (3 H, s, OMe), 5.63 (2 H, s, CH_2) and 7.82 (1 H, s, 5-H)
11	CO_2H	71.5	158.5–159.5 (with decomp.) (A)[c]	CO_2				235	$C_5H_6BrN_3O_3$	25.4	2.6	17.8	3.50 (3 H, s, OMe), 5.68 (2 H, s, CH_2) and 8.50 (1 H, s, exchangeable, OH) (in $CDCl_3$–[$^2H_6$]DMSO)
12	$C(OH)Ph_2$	93	147–148 (B)	Ph_2CO	54.6	4.2	11.35		$C_{17}H_{16}BrN_3O_2$	54.6	4.3	11.2	3.40 (3 H, s, OMe), 3.58 (1 H, s, exchangeable, OH), 5.52 (2 H, s, CH_2) and 7.33 (10 H, m, ArH)
13	SMe	86.5	90–100 at 0.1	Me_2S_2	25.1	4.0	18.0		$C_5H_8BrN_3OS$	25.2	3.4	17.65	2.46 (3 H, s, SMe), 3.43 (3 H, s, OMe) and 5.76 (2 H, s, CH_2)
14	SPh	71	128–132 at 0.6[d]	Ph_2S_2	40.5	3.4	13.8		$C_{10}H_{10}BrN_3OS$	40.0	3.4	14.0	3.40 (3 H, s, OMe), 5.53 (2 H, s, CH_2) and 7.25 (5 H, m, ArH)

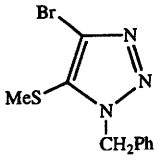
[a] Solvents of crystallisation: A = methanol–dichloromethane; B = light petroleum–ethyl acetate. [b] In $CDCl_3$ unless stated otherwise. [c] The crude acid was extracted from the combined organic layer and ethereal extracts with 2.0 mol dm^{-3} sodium hydroxide (3 × 40 cm^3) then precipitated with 6.0 mol dm^{-3} hydrochloric acid and extracted with ether (2 × 50 cm^3); we were unable to obtain satisfactory microanalytical data. [d] Chromatographed on silica; light petroleum eluted diphenyl disulfide and light petroleum–ethyl acetate (4:1) eluted the product as a pale green oil.

Table 2 4,5-Disubstituted 2-methoxymethyl-2*H*-1,2,3-triazoles

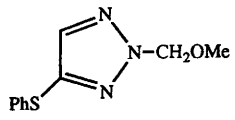


Compound	R	Yield (%)	Mp[a] or bp (*T*/°C, mmHg)	Reagent	Found (%) C	H	N	Formula	Required (%) C	H	N	δ_H(assignment)[b]
16	H	91	70–75 at 0.3	H_2O	25.65	3.3	21.6	$C_4H_6BrN_3O$	25.0	3.15	21.9	3.38 (3 H, s, OMe), 5.57 (2 H, s, CH_2) and 7.65 (1 H, s, 5-H)
17	CO_2Me	71	69–71 (A)[c]	$ClCO_2Me$	28.9	3.3	17.2	$C_6H_8BrN_3O_3$	28.8	3.2	16.8	3.46 (3 H, s, OMe), 3.98 (3 H, s, CO_2Me) and 5.63 (2 H, s, CH_2)
18	$C(OH)Ph_2$	77	78–79 (B)	Ph_2CO	54.5	4.3	11.5	$C_{17}H_{16}BrN_3O_2$	54.6	4.3	11.2	3.52 (3 H, s, OMe), 5.48 (2 H, s, CH_2), 6.16 (1 H, s, exchangeable, OH) and 7.33 (5 H, m, ArH) (in $CDCl_3$–[$^2H_6$]DMSO)
19	SMe	76	80–90 at 0.1	Me_2S_2	25.2	3.4	17.7	$C_5H_8BrN_3OS$	25.2	3.4	17.65	2.56 (3 H, s, SMe), 3.45 (3 H, s, OMe) and 5.60 (2 H, s, CH_2)
20	SPh	75	138–142 at 0.35[d]	Ph_2S_2	40.5	3.3	14.2	$C_{10}H_{10}BrN_3OS$	40.0	3.4	14.0	3.40 (3 H, s, OMe), 5.53 (2 H, s, CH_2) and 7.25 (5 H, m, ArH)

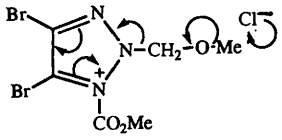
[a] Solvents of crystallisation: A = light petroleum–dichloromethane; B = light petroleum–ether. [b] In $CDCl_3$ unless stated otherwise. [c] Triturated with light petroleum–ether to give a white solid prior to crystallisation; ν_{max}/cm^{-1} 1730 (CO). [d] The combined organic layer and ethereal extracts were washed with 2.0 mol dm^{-3} sodium hydroxide (2 × 40 cm^3), then water (40 cm^3) prior to being dried ($MgSO_4$): the product was chromatographed on silica; light petroleum eluted diphenyl disulfide, then light petroleum–ethyl acetate (4:1) eluted the product.



23 (91.5%)



24 (47%)



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resulting triazol-4-yllithium compound quenched with water, to give a 47% yield of 2-methoxymethyl-4-phenylsulfanyl-2*H*-1,2,3-triazole **24**.

The same high yields of the methylsulfanyl product **23** were obtained when 1-benzyl-4,5-dibromo-1*H*-1,2,3-triazole **1** was reacted with one equivalent of butyllithium (Et_2O, −70 to −80 °C) and the reactions were quenched with dimethyl disulfide after either 15 or 60 min, thus indicating that the initial Br ⟶ Li exchange process is fast. If these reactions were carried out at higher temperatures the isolated yields of product **23** fell with increasing temperature, the reaction mixtures became darker in colour and TLC analysis of the products showed them to be more and more complex. These results can be explained by the onset of ring-opening reactions (see before) at the higher temperatures. Similar yields obtained from reactions carried out in diethyl ether or tetrahydrofuran; 1-benzyl-4,5-dibromo-1*H*-1,2,3-triazole **1** is more soluble in the latter solvent. Reactions could be conducted at temperatures as low as −110 °C without affecting yields significantly.

For the synthesis of methyl 4-bromo-2-methoxymethyl-2*H*-1,2,3-triazole-5-carboxylate **17** we investigated the effectiveness of other organolithium reagents in the Br ⟶ Li exchange reaction. Phenyllithium (from bromobenzene and butyllithium) reacted with compound **7** (Et_2O, −90 to −100 °C) to give a lithium derivative which was quenched after 20 min with one equivalent of methyl chloroformate. Work-up in the usual way gave a separable [by chromatography on silica; light petroleum–ethyl acetate (7:3) eluted the products] mixture of starting material **7** (30% isolated yield) and product **17** (45%). Thus, butyllithium appears to be more effective than phenyllithium in this Br ⟶ Li exchange reaction.

When a similar reaction was carried out with methyllithium, a separable [light petroleum–ethyl acetate (9:1) as eluent] mixture was obtained of starting material **7** (46.5% isolated yield), product **17** (15%) and methyl 4,5-dibromo-1*H*-1,2,3-triazole-1-carboxylate **5** (~2%). The ester **5** was identical in all respects with an authentic sample prepared from 4,5-dibromo-1*H*-1,2,3-triazole and methyl chloroformate (see Experimental section). We suggest that this product arises *via* a 'switching' reaction[16] whereby the starting material **7** reacts at N-1 with methyl chloroformate to produce a quaternary salt **25** which is dealkylated by chloride anion either as shown or by attack of chloride ion on the methylene group with release of chloromethyl methyl ether.

The Grignard reagent **22** was prepared by a reaction between 4-bromo-2-methoxymethyl-2*H*-1,2,3-triazol-5-yllithium, prepared as described before, and anhydrous magnesium bromide. When the reaction mixture was quenched with methyl chloroformate and worked up in the usual way, we obtained a separable mixture of ester **17** (39%) and 4-bromo-2-methoxymethyl-2*H*-1,2,3-triazole **16** (27%). The Li ⟶ MgBr exchange process was conducted at −90 to −100 °C prior to quenching with methyl chloroformate, which probably accounts for this low yield.

Experimental

IR spectra were recorded with a Perkin-Elmer 257 spectrometer (liquids as thin films and solids as Nujol mulls between sodium chloride plates); ^{1}H NMR spectra were recorded with a Varian Associates A60 instrument (at 60 MHz) with tetramethylsilane (TMS) as internal standard (*J* values are given in Hz); ^{13}C NMR spectra were recorded with a Varian Associates CFT20 instrument (at 20 MHz) with TMS as internal standard; and low-resolution mass spectra (EI) were recorded with a Kratos Concept 1S mass spectrometer. Molecular weights obtained by low-resolution mass spectrometry are given for the ^{79}Br isotope; the isotopic abundance ratios were as expected for compounds containing bromine.

Polygram® SIL G/UV_{254} precoated plastic sheets were used for TLC.

All reactions involving organolithium reagents were carried out under dry, oxygen-free nitrogen or argon and all solvents and reagents were dried by standard procedures. Reagents were transferred with syringes through a rubber septum cap fitted to the reaction vessel.

Light petroleum refers to the fraction of bp 40–60 °C unless stated otherwise. Ether refers to diethyl ether. In all cases organic extracts were combined, dried ($MgSO_4$), filtered and evaporated under reduced pressure with a rotary evaporator.

Small-scale distillations were carried out with a Kugelrohr microdistillation apparatus and the 'bp' temperature recorded is that of the oven at the time of distillation. Mps were recorded in open capillary tubes with a Gallenkamp digital melting point apparatus.

Microanalytical results (for C, H and N) were supplied by Butterworth Laboratories of Teddington.

Preparation of starting materials

A chloroform solution of hydrazoic acid (**CAUTION**: the pure compound is extremely toxic and potentially explosive!) was prepared and its concentration (4–10%) determined as described by Wolff.[31] Propiolic acid was prepared as described by Wolf[32] by oxidation of prop-2-yn-1-ol. Addition of hydrazoic acid to the propiolic acid gave 1*H*-1,2,3-triazole-4-carboxylic acid (70%), mp 218–222 °C (from water) (lit.,[22] 71%, mp 222–224 °C), ν_{max}/cm^{-1} 1710 (CO), 2500–3000 (OH) and 3340 (NH), which was bromodecarboxylated[5,19] using the same conditions as those used to brominate 1,2,3-triazole (see later) except that, after addition of the second aliquot of bromine, the solution was maintained at 40–45 °C for 4 h before filtering off the second crop of product, to give 4,5-dibromo-1,2,3-triazole (90–95%), mp 192–194 °C (from aqueous methanol) (lit.,[19] mp 194 °C).

Benzyl azide[25,33] (>90%) (**CAUTION**: the literature preparation[33] advises purification by distillation! In our opinion, because this compound is potentially explosive, on no account should it be purified in this way but by column chromatography on alumina instead. We found that this recipe delivers benzyl azide in a purity high enough for use in the next step[25]) was treated with acetylenedicarboxylic acid [prepared in 80–85% yield by the method of Abbot *et al.*[34] through dehydrobromination of 2,3-dibromosuccinic acid, mp 175–177 °C (from acetone) (lit.,[34] 73–88% yield, mp 175–176 °C)], in acetone to give 1-benzyl-1*H*-1,2,3-triazole-4,5-dicarboxylic acid (96%), mp 181–183 °C (from methanol) (lit.,[25] 92.5%, mp 183 °C). This was decarboxylated by heating it at 170–175 °C and 10–15 mmHg according to the method of Wiley *et al.*,[25] to give 1-benzyl-1*H*-1,2,3-triazole (94%), mp 59–60 °C (from chloroform–light petroleum) (lit.,[25] 85–98%, mp 61 °C).

1-(4-Methoxybenzyl)-1*H*-1,2,3-triazole-4,5-dicarboxylic acid
4-Methoxybenzyl azide[35] (50.5 g, 0.310 mol) (**CAUTION**: potentially explosive!) was added dropwise to a stirred solution of acetylenedicarboxylic acid (35.0 g, 0.307 mol) in acetone at ambient temperature, then the resulting mixture was heated under reflux for 36 h. The solvent was distilled off under reduced pressure to give the product (72.13 g, 84%) as a white solid, mp 157–159 °C (from acetone–hexane), ν_{max}/cm^{-1} 1750 (CO) and 2500–3000 br (OH); $\delta_H(CDCl_3$–[$^2H_6$]DMSO) 3.53 (3 H, s, OMe), 5.87 (2 H, s, CH_2), 6.75 (2 H, d, *J* 7.5, ArH), 7.25 (2 H, d, *J* 7.5, ArH) and 14.07 (2 H, br s, exchangeable, 2 × CO_2H) (Found: C, 51.8; H, 4.0; N, 15.0. $C_{12}H_{11}N_3O_5$ requires C, 52.0; H, 4.0; N, 15.15%).

1-(4-Methoxybenzyl)-1*H*-1,2,3-triazole
1-(4-Methoxybenzyl)-1*H*-1,2,3-triazole-4,5-dicarboxylic acid (20.0 g, 72.0 mmol) was heated at 155 °C (oil bath) and 1.4 mmHg when a vigorous reaction started. Heating was discontinued and the reaction was left until evolution of carbon dioxide had ceased. The brown solid residue (12.96 g, 95% crude) was crystallised from light petroleum–dichloromethane (6:4) to give the product as white crystals, mp 92–93 °C (lit.,[26] 89–91 °C); δ_H 3.78 (3 H, s, OMe), 5.45 (2 H, s, CH_2), 6.80 (2 H, d, *J* 7.5, ArH), 7.10 (2 H, d, *J* 7.5, ArH), 7.40 (1 H, s, 5-H) and 7.60 (1 H, s, 4-H) (Found: C, 62.9; H, 5.9; N, 22.5. $C_{10}H_{11}N_3O$ requires C, 63.5; H, 5.9; N, 22.2%).

1,2,3-Triazole
Method A. (Variation of the method of Wiley *et al.*[25]) An autoclave charged with 1-benzyl-1*H*-1,2,3-triazole (130.0 g, 0.817 mol), dioxane (200 cm^3), 10% palladium–charcoal (13 g) and hydrogen was kept at 110 °C and 70 atm for 3 h, after which it was cooled and the catalyst filtered off. The filtrate was concentrated to *ca.* 50 cm^3 by distillation of the solvent on a rotary evaporator, and addition of light petroleum to the residual solution formed two layers. The lower layer was separated and distilled (Kugelrohr apparatus), bp 70–80 °C at 1–1.5 mmHg (**CARE**: see ref. 25), to give 1,2,3-triazole (41.7 g, 74%) (lit.,[25] 47%, bp 208–210 °C at 760 mmHg), δ_H 7.83 (NH proton not detectable).

Method B. 1-(4-Methoxybenzyl)-1*H*-1,2,3-triazole (9.45 g, 50.0 mmol) was dissolved in trifluoroacetic acid (30 cm^3), anisole (1 cm^3) was added and the resulting mixture was stirred and heated under reflux for 4 h, then cooled. The excess of trifluoroacetic acid was distilled off under reduced pressure to give 1,2,3-triazolium trifluoroacetate (7.14 g, 78%) as an off-white solid, mp 75–78 °C [from light petroleum–acetone (2:8)]; $\delta_H(CDCl_3)$ 7.80 (2 H, s, ArH) and 14.53 (2 H, br s, exchangeable, 2 × NH) (Found: C, 26.4; H, 2.3; N, 23.4. $C_4H_4F_3N_3O_2$ requires C, 26.2; H, 2.2; N, 22.95%). This salt was treated with an excess of saturated aqueous sodium hydrogen carbonate and the product was extracted with ether, to give 1,2,3-triazole (100%) identical in all respects with the sample prepared as described in Method A.

4,5-Dibromo-1*H*-1,2,3-triazole
(Variation of the method of Hüttel and Gebhardt.[19]) Bromine (15 cm^3, an excess) was added dropwise to a stirred solution of 1,2,3-triazole (15.0 g, 217 mmol) in water (100 cm^3) warmed to 40–45 °C and the resulting solution was stirred for a further 1 h. The precipitate was filtered off and further bromine (10 cm^3) was added to the filtrate, then it was kept at ambient temperature overnight, after which a second crop of product had precipitated. The combined amounts of product were washed with water (3 × 50 cm^3), dried and recrystallised from aqueous methanol, to give 4,5-dibromo-1*H*-1,2,3-triazole (47.8 g, 97%), mp 192–194 °C (lit.,[19] 95%, mp 194 °C).

1-Benzyl-4,5-dibromo-1*H*-1,2,3-triazole 1
Benzyl chloride (1.27 g, 1.15 cm^3, 10.0 mmol) was added to a stirred mixture of 4,5-dibromo-1*H*-1,2,3-triazole (2.27 g, 10.0 mmol) and triethylamine (1.11 g, 1.5 cm^3, 11.0 mmol) in dichloromethane (50 cm^3) at ambient temperature and the resulting mixture was stirred at this temperature for a further 3 h. The solvent was distilled off under reduced pressure and water (100 cm^3) was added to the residue. Extraction with chloroform (3 × 40 cm^3) gave 1-*benzyl*-4,5-*dibromo*-1H-1,2,3-*triazole* **1** (1.01 g, 32%), as a white solid; mp 99–101 °C (from ethyl acetate–light petroleum); $\delta_H(CDCl_3)$ 5.53 (2 H, s, CH_2) and 7.33 (5 H, m, ArH); δ_C([$^2H_6$]DMSO) 53.36 (t, CH_2), 113.76 (s, C-5), 122.70 (s, C-4), 127.63 (d, C-4′), 128.37 (d, C-3′/5′), 128.83 (d, C-2′/6′) and 134.16 (s, C-1′) (Found: C, 34.5; H, 2.2; N, 13.8. $C_9H_7Br_2N_3$ requires C, 34.1; H, 2.2; N, 13.3%).

4,5-Dibromo-1-(4-methoxybenzyl)-1*H*-1,2,3-triazole 2
As for **1**, using 4-methoxybenzyl chloride, to give a white solid (22%); mp 101–103 °C (from ethyl acetate–light petroleum); $\delta_H(CDCl_3)$ 3.78 (3 H, s, OMe), 5.47 (2 H, s, CH_2), 6.83 (2 H, d, *J* 7.5, ArH) and 7.45 (2 H, d, *J* 7.5, ArH) (Found: C, 34.4; H, 2.7; N, 12.2. $C_{10}H_9Br_2N_3O$ requires C, 34.6; H, 2.6; N, 12.1%).

Reaction of 4,5-dibromo-1*H*-1,2,3-triazole with 4-nitrobenzyl chloride
As for **1**, using 4-nitrobenzyl chloride (1.72 g, 10.0 mmol) in place of the benzyl chloride, to give a mixture of two isomeric compounds (2.45 g, 68%) (ratio 45:55 by integration of CH_2 signals in ^1H NMR spectrum) which was chromatographed on silica using chloroform as eluent.

4,5-Dibromo-2-(4-nitrobenzyl)-2*H*-1,2,3-triazole 6. First fraction (0.94 g, 26%) as a white solid, mp 116–118 °C [from ethyl acetate–light petroleum (2:8)]; $\delta_H(CDCl_3)$ 5.63 (2 H, s, CH_2), 7.45 (2 H, d, *J* 8.0, ArH) and 8.16 (2 H, d, *J* 8.0, ArH); $\delta_C(CDCl_3)$ 58.69 (t, CH_2), 123.86 (d, C-3′/5′), 125.22 (s, C-4/5), 128.88 (d, C-2′/6′), 140.36 (s, C-1′) and 147.81 (s, C-4′) (Found: C, 29.9; H, 1.7; N, 15.9. $C_9H_6Br_2N_4O_2$ requires C, 29.9; H, 1.7; N, 15.5%).

4,5-Dibromo-1-(4-nitrobenzyl)-1*H*-1,2,3-triazole 3. Second fraction (1.05 g, 29%) as a white solid, mp 160–162 °C [from chloroform–light petroleum (3:7)]; $\delta_H(CDCl_3)$ 5.67 (2 H, s, CH_2), 7.52 (2 H, d, *J* 8.0, ArH) and 8.10 (2 H, d, *J* 8.0, ArH) (Found: C, 29.8; H, 1.8; N, 15.6%).

Reaction of 4,5-dibromo-1*H*-1,2,3-triazole and chloromethyl methyl ether
Chloromethyl methyl ether (**CAUTION**: carcinogenic!) (4.43 g, 4.2 cm^3, 55.0 mmol) was added dropwise to a stirred solution of 4,5-dibromo-1*H*-1,2,3-triazole (11.35 g, 50.0 mmol) and triethylamine (5.57 g, 7.7 cm^3, 55.0 mmol) in anhydrous benzene (**CAUTION**: potentially carcinogenic!) (200 cm^3) at ambient temperature and the resulting mixture was stirred for a further 3 h, then the solvent was distilled off under reduced pressure and water (150 cm^3) added to the residue. Extraction with chloroform (3 × 50 cm^3) gave a pale yellow oil (11.38 g, 84%), shown by ^1H NMR spectroscopy to be a mixture of two isomers (ratio 45:55), which was chromatographed on silica using light petroleum–ethyl acetate (8:2).

4,5-Dibromo-2-methoxymethyl-2*H*-1,2,3-triazole 7. First fraction (4.15 g, 31%) as a colourless oil, bp (Kugelrohr) 90–95 °C at 0.25 mmHg which solidified, mp 33–34 °C; $\delta_H(CDCl_3)$ 3.50 (3 H, s, OMe) and 5.60 (2 H, s, CH_2); $\delta_C(CDCl_3)$ 57.63 (q, OMe), 84.74 (t, CH_2O) and 125.85 (s, C-4/5) (Found: C, 18.0; H, 1.6; N, 15.6. $C_4H_5Br_2N_3O$ requires C, 17.7; H, 1.9; N, 15.5%).

4,5-Dibromo-1-methoxymethyl-1*H*-1,2,3-triazole 4. Second fraction (4.57 g, 34%) as a colourless oil, bp (Kugelrohr) 95–100 °C at 0.3 mmHg, which solidified on standing, mp 35–37 °C; $\delta_H(CDCl_3)$ 3.43 (s, OMe) and 5.69 (2 H, s, CH_2O); $\delta_C(CDCl_3)$ 57.01 (q, OMe), 79.58 (t, CH_2O), 112.56 (s, C-5) and 123.28 (s, C-4) (Found: C, 17.9; H, 1.8; N, 15.8%).

4,5-Dibromo-2-triphenylmethyl-1*H*-1,2,3-triazole 8

Triphenylmethyl chloride (12.3 g, 44.0 mmol) was added to a stirred mixture of 4,5-dibromo-1*H*-1,2,3-triazole (10.0 g, 44.0 mmol) and triethylamine (5.06 g, 7.0 cm^3, 50.0 mmol) in anhydrous benzene (70 cm^3) at ambient temperature and the resulting mixture was stirred at this temperature for a further 2.5 h. The solvent was removed under reduced pressure and water (150 cm^3) was added to the residue. Extraction with chloroform (3 × 75 cm^3) gave the *product* **8** (18.77 g, 91%) as a white solid, mp 199–200 °C [from dichloromethane–light petroleum (2:8)]; $\delta_H(CDCl_3)$ 7.20 (15 H, m, ArH) (NH signal not detectable); $\delta_C(CDCl_3$–[$^2H_6$]DMSO) 84.02 (s, *C*Ph_3), 124.02 (s, C-4/5), 127.19 (d, C-4′), 127.67 (d, C-3′/5′), 129.75 (d, C-2′/6′) and 141.12 (s, C-1′) (Found: C, 54.0; H, 3.3; N, 8.9. $C_{21}H_{15}Br_2N_3$ requires C, 53.8; H, 3.2; N, 9.0%).

4,5-Dibromo-2-hydroxymethyl-2*H*-1,2,3-triazole 9

A pale yellow mixture of 4,5-dibromo-1-methoxymethyl-1*H*- and -2-methoxymethyl-2*H*-1,2,3-triazole (**4** and **7**) as an oil was kept for 3 months in a stoppered flask in daylight at ambient temperature. The white crystalline solid which separated was filtered off and recrystallised from acetone–light petroleum (4:6), to give the *hydroxymethyl compound* **9**, mp 125–127 °C; ν_{max}/cm^{-1} 3360 (OH); $\delta_H(CDCl_3$–[$^2H_6$]DMSO) 5.60 (2 H, d, CH_2) and 7.42 (1 H, t, exchangeable, OH); δ_C([$^2H_6$]DMSO) 77.71 (t, *C*H_2) and 124.69 (s, C-4/5) (Found: C, 14.4; H, 1.15; N, 16.5%; M^+, 255. $C_3H_3Br_2N_3O$ requires C, 14.0; H, 1.2; N, 16.4%; *M*, 255).

General procedure for synthesis of polysubstituted 1,2,3-triazoles 10–14 and 16–20 *via* bromine ⟶ lithium exchange

Butyllithium (1.7 mol dm^{-3} in hexane; 11.9 cm^3, 20.0 mmol) was added dropwise to a stirred solution of 4,5-dibromo-1-methoxymethyl-1*H*- or -2-methoxymethyl-2*H*-1,2,3-triazole (**4** or **7**) (5.0 g, 18.5 mmol) in ether (150 cm^3) at −70 to −80 °C at such a rate that this temperature was maintained. The resulting mixture was stirred for a further 20 min, then a suitable quenching reagent (20.0 mmol) was added (for replacement of Br by H an excess of aqueous ammonium chloride was added; for replacement by CO_2H dried carbon dioxide gas was bubbled through the solution; other reagents were added as solutions in ether, dropwise) and stirring was continued at −70 to −80 °C for a further 20–60 min (reaction followed by TLC). The mixture was allowed to warm up to ambient temperature, and saturated ammonium chloride (100 cm^3) was added (except in the case of replacement of Br by H). The organic layer and ethereal extracts were combined, dried ($MgSO_4$) and distillation of the solvent under reduced pressure gave the product which was either distilled, recrystallised or chromatographed on silica (see Tables 1 and 2 for details of products).

1-Benzyl-4-bromo-5-methylsulfanyl-1*H*-1,2,3-triazole 23

Butyllithium (1.7 mol dm^{-3} in hexane; 3.25 cm^3, 5.5 mmol) was added dropwise to a stirred solution of 1-benzyl-4,5-dibromo-1*H*-1,2,3-triazole **1** (1.60 g, 5.0 mmol) in ether (100 cm^3) at −70 to −80 °C and the resulting mixture was stirred for a further 40 min. Dimethyl disulfide (0.52 g, 0.5 cm^3, 5.5 mmol) in ether (2 cm^3) was added and the mixture was stirred at −70 to −80 °C for a further 1 h, then allowed to warm up to ambient temperature. Saturated aqueous ammonium chloride (50 cm^3) was added, the organic layer was separated and the aqueous layer was extracted with ether (2 × 40 cm^3). The combined organic layer and ethereal extracts were dried ($MgSO_4$) and the solvent was distilled off under reduced pressure to give a pale yellow solid (1.30 g, 91.5%) which was recrystallised from ethyl acetate–light petroleum, to give the *product* **23** as a white solid, mp 70–71 °C; δ_H 2.05 (3 H, s, SMe), 5.60 (2 H, s, CH_2) and 7.33 (5 H, m, ArH) (Found: C, 42.0; H, 3.5; N, 15.0. $C_{10}H_{10}BrN_3S$ requires C, 42.3; H, 3.55; N, 14.8%).

2-Methoxymethyl-4-phenylsulfanyl-2*H*-1,2,3-triazole 24

Butyllithium (1.5 mol dm^{-3} in hexane; 10.8 cm^3, 16.0 mmol) was added dropwise to a stirred solution of 4,5-dibromo-2-methoxymethyl-2*H*-1,2,3-triazole **7** (4.0 g, 15.0 mmol) in ether (75 cm^3) at −90 to −100 °C and the resulting mixture was stirred at this temperature for a further 30 min. Then diphenyl disulfide (3.48 g, 16.0 mmol) in ether (320 cm^3) was added dropwise at such a rate that the temperature was maintained at −90 to −100 °C. After 30 min the mixture was allowed to warm up to ambient temperature, then it was cooled again to − 90 to −100 °C when a further quantity of butyllithium (1.5 mol dm^{-3}; 10.8 cm^3, 16.0 mmol) was added. After a further 20 min, saturated aqueous ammonium chloride (50 cm^3) was added cautiously and the mixture was allowed to warm up again to ambient temperature. The organic layer was separated and the aqueous layer extracted with ether (2 × 40 cm^3). The organic layer and ethereal extracts were combined, dried ($MgSO_4$) and distillation of the solvent under reduced pressure gave a brown oil which was chromatographed on silica. Dichloromethane–light petroleum (2:8) eluted diphenyl disulfide (1.32 g) followed by *2-methoxymethyl-4-phenylsulfanyl*-2H-1,2,3-*triazole* **24** (1.54 g, 47%) as a colourless oil, bp 126–131 °C at 0.6 mmHg; $\delta_H(CDCl_3)$ 3.40 (3 H, s, OMe), 5.57 (2 H, s, CH_2), 7.30 (5 H, m, ArH) and 7.60 (1 H, s, 4-H) (Found: C, 54.4; H, 5.1; N, 19.25. $C_{10}H_{11}N_3OS$ requires C, 54.4; H, 5.0; N, 19.0%).

Methyl 4,5-dibromo-1*H*-1,2,3-triazole-1-carboxylate 5

Methyl chloroformate (1.32 g, 1.1 cm^3, 14.0 mmol) was added to a stirred mixture of 4,5-dibromo-1*H*-1,2,3-triazole (3.0 g, 13.0 mmol), dichloromethane (40 cm^3) and triethylamine (1.32 g, 1.8 cm^3, 13.0 mmol) at ambient temperature and the resulting mixture was stirred overnight, then water (100 cm^3) was added and the organic layer was separated off. The aqueous layer was extracted with dichloromethane (2 × 50 cm^3), then the organic layer and extracts were combined, dried ($MgSO_4$) and distillation of the solvent under reduced pressure gave the *product* **5** (2.70 g, 73%) as a white solid, mp 143–145 °C (from ether–dichloromethane), ν_{max}/cm^{-1} 1750 (CO); $\delta_H(CDCl_3$–[$^2H_6$]DMSO) 4.21 (3 H, s, CO_2Me); $\delta_C(CDCl_3$–[$^2H_6$]DMSO) 56.01 (q, Me), 123.76 (s, C-4), 130.84 (s, C-5) and 160.01 (s, N-C) (Found: C, 16.6; H, 1.0; N, 14.8. $C_4H_3Br_2N_3O_2$ requires C, 16.9; H, 1.1; N, 14.75%).

Synthesis of 4-bromo-2-methoxymethyl-2*H*-1,2,3-triazol-5-ylmagnesium bromide 22 and its reaction with methyl chloroformate

Butyllithium (1.3 mol dm^{-3} in hexane; 9.3 cm^3, 12.0 mmol) was added dropwise to a stirred solution of 4,5-dibromo-2-methoxymethyl-2*H*-1,2,3-triazole **7** (3.0 g, 11.1 mmol) in ether (75 cm^3) at −90 to −100 °C at such a rate that this temperature was maintained, then the resulting mixture was stirred for a further 30 min. Anhydrous magnesium bromide (2.24 g, 12.0 mmol) was added and stirring was continued for a further 30 min at −90 to −100 °C prior to addition of methyl chloroformate (1.25 g, 1.02 cm^3, 13.0 mmol). After 30 min the mixture was allowed to warm up to ambient temperature and quenched by addition of an excess of saturated aqueous ammonium chloride. Work-up as described before gave a yellow oil which was chromatographed on silica. Light petroleum–ethyl acetate (6:4) eluted 4-bromo-2-methoxymethyl-2*H*-1,2,3-triazole **16** (0.58 g, 27%) as a colourless oil, identical (^1H and ^{13}C NMR spectra and TLC) with the sample prepared as described before, and methyl 4-bromo-2-methoxymethyl-2*H*-1,2,3-triazole-5-carboxylate **17** (1.09 g, 39%), also identical (mp, ^1H and ^{13}C NMR spectra and TLC) with the sample prepared as described before.

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