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PAPER

Deproto-metallation and computed CH acidity of 2-aryl-1,2,3-triazoles†

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2-Aryl-1,2,3-triazoles were synthesized by cyclization of the corresponding glyoxal arylosazones, generated from commercial arylhydrazines. The deproto-metallation of 2-phenyl-1,2,3-triazole was attempted using different 2,2,6,6-tetramethylpiperidino-based mixed lithium–metal (Zn, Cd, Cu, Co, Fe) combinations, giving results in the case of Zn, Cd, and Cu. The lithium–zinc combination was next selected to apply the deprotonation–iodination sequence to all the 2-aryl-1,2,3-triazoles synthesized. The results were analyzed with the help of the CH acidities of the substrates, determined in THF solution using the DFT B3LYP method.

Introduction

1,2,3-Triazoles have been shown to exhibit a broad spectrum of biological activities, and have found applications as agrochemicals, dyes, anticorrosive agents and photographic materials.[1] Even if less described than 1-aryl-1,2,3-triazoles, probably in relation with a lack of general synthetic methods,[2] 2-aryl-1,2,3-triazoles have found applications, for example as optical brighteners.[3]

Deprotonative lithiation is an efficient tool to functionalize regioselectively heterocycles;[4] concerning 1,2,3-triazoles, such a possibility has been developed using as substrates 1-substituted 1,2,3-triazoles, affording after subsequent trapping 5-substituted derivatives.[5] The reason why no direct lithiation of 2-substituted 1,2,3-triazoles has been documented could be in relation to the possible ring opening of the metallated species in this case (Scheme 1, S = substituent).

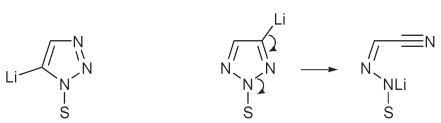
Combinations of lithium reagents and softer metal compounds have recently emerged as efficient tools to deproto-metallate sensitive aromatic compounds.[6] In search of new bimetal bases for tricky deproto-metallations, we developed the use of TMP-based (TMP = 2,2,6,6-tetramethylpiperidino) lithium–zinc,[7–10] lithium–cadmium,[9,11] lithium–copper(I),[12,13] lithium–cobalt[14] and lithium–iron[15] mixtures, prepared by mixing LiTMP with MCl_2·TMEDA (1/3 equiv, M = Zn, Cd or Cu, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), CuCl (1/2 equiv), $CoBr_2$ (1/3 equiv) or $FeBr_2$ (1/3 equiv).

We herein describe our attempts to use these lithium–metal combinations for the deproto-metallation of 2-aryl-1,2,3-triazoles. The regioselectivity of the reaction being partly determined by the acidity of the different hydrogens in the substrate molecule, the CH acidities of the triazole substrates in THF were calculated within the density functional theory (DFT) framework using a homodesmic reaction approach described previously,[10,16–18] and were used to rationalize the outcome of the reactions.

Results and discussions

Synthetic aspects

While syntheses of 1-aryl-1,2,3-triazoles have largely been described, notably using thermal and Cu(I)- or Ru(II)-catalyzed cycloaddition reactions from alkynes and azides, few ways exist to synthesize 2-aryl-1,2,3-triazoles.[2]



Scheme 1 Compared stabilities of the lithio derivatives of 1-substituted 1,2,3-triazoles and 2-substituted 1,2,3-triazoles.

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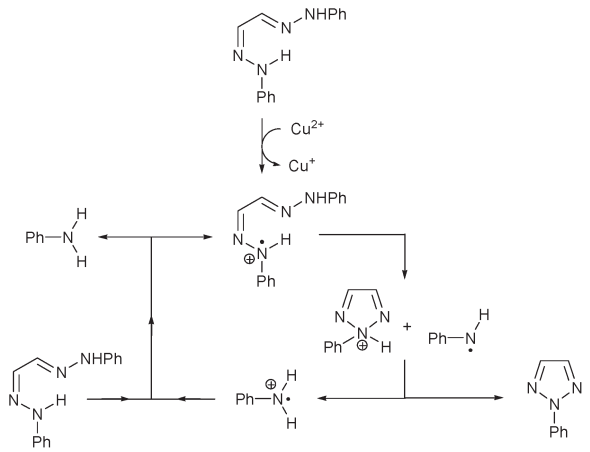
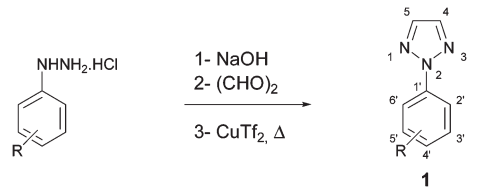
†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra, gas phase acidities of the investigated triazoles and Cartesian coordinates of molecular geometry for the most stable rotamer forms of the investigated aryltriazoles (neutral molecule, gas phase) optimized at B3LYP/6-31G(d) level of theory. CCDC 864272–864279. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25554e



Scheme 2 Mechanism proposed to rationalize the Cu(II)-catalyzed cyclization of glyoxal phenylosazone.

Table 1 Synthesis of the 2-aryl-1,2,3-triazoles **1**



Entry	R	Product, yield[a] (%)
1	H	**1a**, 82
2	4′-Me	**1b**, 50
3	4′-^{i}Pr	**1c**, 61
4	4′-OMe	**1d**, 64
5	3′-Cl	**1e**, 88

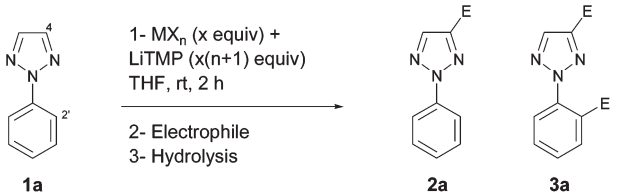
[a] Overall yield over three steps.

We considered for this purpose the cyclization of glyoxal bis-(aryl)hydrazones (glyoxal arylosazones), generated from commercial arylhydrazines. The Cu(II)-catalyzed method developed by Myachina and co-workers in the case of phenylhydrazine,[19,20] and for which we propose the one electron mechanism shown in Scheme 2, was followed.

In the presence of catalytic copper(II) triflate, the reaction was performed either at 150 °C without solvent (Table 1, entries 1, 2 and 5) or at toluene reflux (Table 1, entries 3 and 4) to furnish the expected derivatives **1a–e** in yields ranging from 50 to 88%.

The abilities of the different lithium–metal combinations to deproto-metallate 2-phenyl-1,2,3-triazole (**1a**) were compared (Table 2). To this purpose, **1a** was first treated with the lithium–zinc base, *in situ* prepared from $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv),[21] in THF for 2 h at room temperature before interception with iodine; under these conditions, two derivatives were isolated, the 4-iodo derivative **2a**, obtained in 38% yield, and the 4,2′-diiodide **3a**, isolated in 7% yield (Table 2, entry 1). The monoiodide **2a** was identified unequivocally by X-ray structure analysis (Fig. 1).† Replacing zinc by cadmium led to an improved conversion and a more important formation of **3a** (Table 2, entry 2); such a dideprotonation using the lithium–

Table 2 Deprotonative metallation of **1a** using different lithium–metal combinations followed by trapping with electrophiles



Entry	MX_n (*x* equiv)	Electrophile (*E*)	Product, yield (%)	
1	$ZnCl_2$·TMEDA (0.5)	I_2 (I)	**2a**, 38	**3a**, 7
2	$CdCl_2$·TMEDA (0.5)	I_2 (I)	**2a**, 46	**3a**, 14
3	CuCl (1)	PhCOCl (PhCO)	**2a′**, 34	*a*
4	$CoBr_2$ (2)	I_2 (I)	*a,b*	*a,b*
5	$FeBr_2$ (1)	^{t}BuCHO (^{t}BuCH(OH))	*a,c*	*a,c*

[a] Not obtained. [b] Degradation of **1a** was noted. [c] **1a** was recovered.

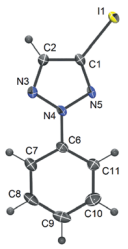


Fig. 1 ORTEP diagram (30% probability) of **2a**.

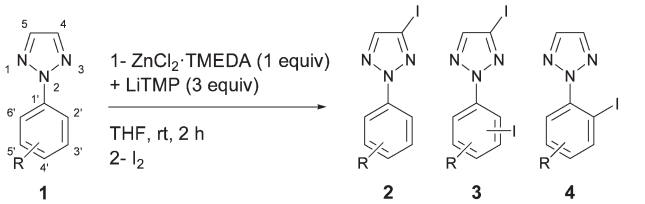
cadmium reagent has previously been observed from different diactivated substrates.[9,11]

Using the lithium–copper base, *in situ* prepared from CuCl (1 equiv) and LiTMP (2 equiv), under the same reaction conditions followed by trapping with benzoyl chloride[22] afforded the phenyl ketone **2a′** in 34% yield (Table 2, entry 3), maybe through the thermodynamic metallated species at C4.[13] On the other hand, using the lithium–cobalt base *in situ* prepared from $CoBr_2$ (2 equiv)[23] and LiTMP (6 equiv) or the lithium–iron base *in situ* prepared from $FeBr_2$ (1 equiv) and LiTMP (3 equiv) led to degradation and starting material, respectively (Table 2, entries 4 and 5).

To avoid concerns about inherent toxicity of cadmium compounds,[24] we decided to pursue the study using the lithium–zinc base, but prepared from $ZnCl_2$·TMEDA (1 equiv) and LiTMP (3 equiv) in order to reach higher conversions (Table 3). Starting from 2-phenyl-1,2,3-triazole (**1a**), the 4,2′-diiodide **3a** was formed in 56% yield, to the detriment of the 4-iodo derivative **2a** which was obtained in 12% yield; quasi-complete conversion and 63% yield for **3a** could even be reached by doubling the amount of base (Table 3, entry 1).

In the presence of a methyl and, above all, an isopropyl group at the 4 position of the phenyl ring (substrates **1b** and **1c**), the 4-iodo derivatives **2b** and **2c** were formed more significantly. However, using $ZnCl_2$·TMEDA (2 equiv) and LiTMP (6 equiv) afforded the 4,2′-diiodide **3b** and **3c** in 58 and 61% yield, respectively (Table 3, entries 2 and 3). In the case of methylated **1b**, the 4,2′-diiodide **3b** as well as the 2′-monoiodo derivative

Table 3 Deprotonative metallation of **1a–e** using mixed Li–Zn base followed by trapping with I_2



Entry	Substrate (*R*)	Product, Yield (%)		
1	**1a** (H)	**2a**, 12 (2)[a]	**3a** (2′-I), 56 (63)[a]	[b]
2	**1b** (4′-Me)	**2b**, 15 (7)[a]	**3b** (2′-I), 32 (58)[a]	**4b**, 13 (6)[a]
3	**1c** (4′-^{i}Pr)	**2c**, 36 (12)[a]	**3c** (2′-I), 7 (61)[a]	[b]
4	**1d** (4′-OMe)	[b]	**3d** (2′-I), 35 (56)[a,c] **3′d** (3′-I), 3 (0)[a,c]	**4d**, 18 (0)[a,c]
5	**1e** (3′-Cl)	**2e**, 6 (0)[a]	**3e** (2′-I), 12 (19)[a] **3′e** (6′-I), 35 (59)[a]	[b]

[a] Deprotonation performed using $ZnCl_2$·TMEDA (2 equiv) + LiTMP (6 equiv). [b] Not obtained. [c] 2-(2,5-Diiodo-4-methoxyphenyl)-4-iodo-1,2,3-triazole (**5d**) was also isolated in 7% yield.

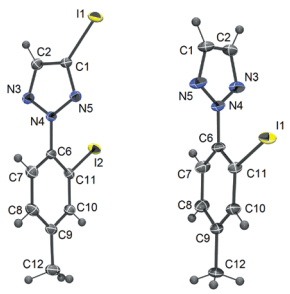


Fig. 2 ORTEP diagrams (30% probability) of **3b** and **4b**.

4b, which was also obtained (6–13% yield), were identified unequivocally by X-ray structure analysis (Fig. 2).† No benzylic deprotonation was evidenced in these experiments.

Anisole being easily *ortho*-deprotonated under similar reaction conditions,[8] it was interesting to involve in the deprotonation–iodination sequence 2-(4-methoxyphenyl)-1,2,3-triazole (**1d**). Due to the activating effect of the methoxy group, a complete conversion was noted but, as suspected, several products were isolated. Using $ZnCl_2$·TMEDA (1 equiv) and LiTMP (3 equiv) afforded the 4,2′-diiodide **3d** (35% yield), the 2′-monoiodide **4d** (18% yield), and the 4,3′-diiodide **3′d** (3% yield); the formation of the former could be improved to 56% yield using $ZnCl_2$·TMEDA (2 equiv) and LiTMP (6 equiv), but under these conditions the 4,2′,5′-triiodide **5d** also formed and was also isolated in 7% yield (Table 3, entry 4). Both the 4,2′-diiodide **3d** and the 4,3′-diiodide **3′d** were identified by X-ray diffraction from suitable crystals (Fig. 3).†

With a chloro group at the 3 position of the phenyl group, things can be more complex due to the loss of symmetry. Upon treatment with the lithium–zinc base prepared from $ZnCl_2$·TMEDA (1 equiv) and LiTMP (3 equiv), 2-(3-chlorophenyl)-1,2,3-triazole (**1e**) was converted to a mixture of the 4,6′-diiodide **3′e** (35% yield), the 4,2′-diiodide **3e** (12% yield) and

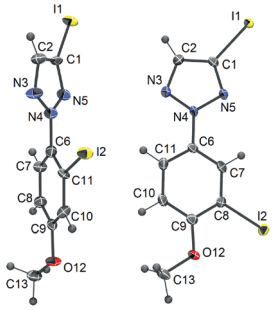


Fig. 3 ORTEP diagrams (30% probability) of **3d** and **3′d**.

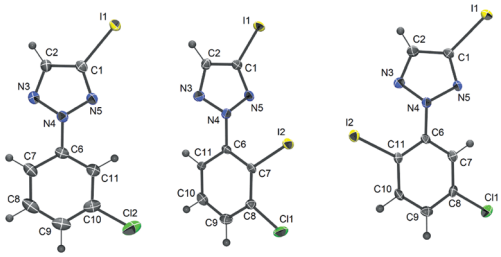


Fig. 4 ORTEP diagrams (30% probability) of **2e** (left), **3e** (middle) and **3′e** (right).

the 4-monoiodide **2e** (6% yield). Increasing the base amount ($ZnCl_2$·TMEDA (2 equiv) and LiTMP (6 equiv)) resulted in the exclusive formation of the diiodides **3′e** and **3e** (59 and 19% yield, respectively) (Table 3, entry 5). The structures of all three derivatives **2e**, **3e**, and **3′e** were confirmed by X-ray analysis (Fig. 4).†

Benzyne formation was previously evidenced using Me_2Zn(TMP)Li as base;[25] in our case, the observed good conversion to iodides shows that the elimination of metal chloride giving benzyne is not the main reaction.

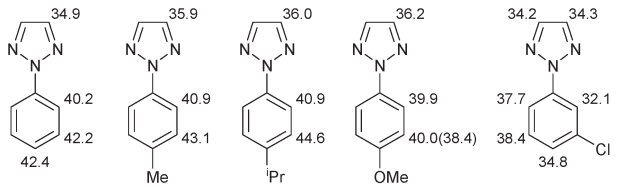
Computational aspects

The data on CH acidity of triazoles are scanty. Fraser reported the value (26.2) for pK_a of 1-propyl-1*H*-1,2,4-triazole in THF solution.[26] Substituent CH acidities in DMSO for ethynyltriazoles were evaluated and compared with the results computed by employing the semi-empirical CNDO 2 method.[27] The CH acidity of some unsubstituted azoles were also estimated recently within the DFT framework.[28]

We showed earlier that DFT calculations provide good results for gas-phase formation enthalpy[29] and basicity[30] of triazoles. In the present paper, the results of DFT calculations of CH acidity of the different 2-aryl-1,2,3-triazoles **1a–e**, both in gas phase (see ESI†) and in THF solution (Scheme 3), are presented.

The gas phase acidities $\Delta_{acid}G$ and pK_a values in THF solution of all the triazole substrates were calculated using a theoretical approach related to the one previously described. We used it successfully to account for mercuration of substituted triazoles,[17] trends in CH acidity of *N*-alkylazoles,[18] reactivity of *N*-aryl pyrazoles[10] and pyridines.[13]

All the calculations were conducted with the Gaussian 03 package[31] using the DFT B3LYP method. The geometries were



Scheme 3 Calculated values of pK_a(THF) of the investigated triazoles.

optimized using the 6-31G(d) basis set (see ESI†). No symmetry constraints were imposed. In order to perform stationary points characterization and to calculate zero-point vibrational energies (ZPVE) and thermal corrections to Gibbs free energy, vibrational frequencies were calculated at the same level of theory. The single point energy calculations were performed using the 6-311+G(d,p) basis set.

The gas phase acidities $\Delta_{acid}G$ were determined as the Gibbs energies of deprotonation of the substrates R − H (R − $H_{(g)}$ → $R^-_{(g)}$ + $H^+_{(g)}$).

The solvent effects were evaluated using the polarized continuum model (PCM) with the default parameters for THF.[32] The PCM energies E_{PCM} were calculated at the B3LYP/6-311+G(d,p) level using geometries optimized for isolated structures. The Gibbs energy in solution G_s was calculated for each species by the formula:

$$G_s = G^0{}_{298} + E_{PCM} - E.$$

To cancel possible inexactnesses, the pK_a values were calculated by means of the following homodesmic reaction:

$$R - H_{(s)} + Het^-{}_{(s)} \rightarrow R^-{}_{(s)} + Het - H_{(s)},$$

where Het−H is a reference compound, 1-propyl-1*H*-pyrazole, stucturally related to the investigated molecules and whose pK_a value in THF (35.9)[26] is supposed to be close to that of aryltriazoles.

The pK_a values were calculated from the Gibbs energies of the homodesmic reactions ($\Delta_r G_s$) using the equation:

$$pK_a(R - H) = 35.9 + \frac{\Delta_r G_s}{RT} \times \frac{1}{\ln 10}$$

The CH acidity of side groups such as alkyl and alkoxy, was expected to be significantly lower and hence was not considered. The results are given below (Scheme 3).

For the compounds **1b** and **1d**, that can exist in the form of several distinct rotamers, the data in Scheme 3 and in ESI† refer to the most stable rotamers. According to our calculations for the investigated aryltriazoles, a significant inequality in CH acidity between the C3′ and C5′ sites adjacent to rotatable substituent was only noticed in the case of the methoxy derivative **1d**.

Overall the CH acidities of the aryltriazoles correlate with the electron-donating or electron-withdrawing effect of the phenyl's substituent. The latter has above all an impact on the reactivity of the six-membered part of the molecule; the triazole ring, which already benefits from high CH acidities, is affected only slightly. The chloro substituent exhibits the most prominent acidifying effect, providing more variants for synthetic pathways.

When the trends in CH acidity of isolated molecules are compared with the pK_as in THF solution, one can see a good correlation, described by the equation:

$$pK_a(THF) = -193.1 + 0.612\ \Delta_{acid}G$$
$$(N = 20, r^2 = 0.948, \text{rmse} = 1.07)$$

Such a good correlation indicates that the polarities (or dipole moments) of the different possible anions are close and that there is no specific solvation. When compared with gas-phase, deprotonation in solution will take place more unlikely at the 3′ position of the substrate.

Discussion

The calculations of the CH acidities in THF (Scheme 3) allowed us to identify several possible deprotonation sites on the 2-aryl-1,2,3-triazole substrates. With the exception of the compound **1e**, for which a 3-chlorophenyl is grafted on the 1,2,3-triazole 2 position, the most acidic site corresponds to the 4 position of the azole ring (α to the triazole nitrogen[4]) whereas the second acidic site corresponds to the 2′ position of the aryl group (*ortho* to the triazole substituent[4]).

In general, the main derivatives obtained are at least iodinated at their most acidic C4 position. Compared with 2-phenyl-1,2,3-triazole (**1a**), the derivatives bearing a methyl and an isopropyl group at the 4 position of the phenyl ring (substrates **1b** and **1c**), (logically) have lower CH acidities in THF solution. Thus, according to calculations, more difficult deproto-metallations are expected from the alkylated substrates; the experimental results using the lithium–zinc base prepared from $ZnCl_2$·TMEDA (1 equiv) and LiTMP (3 equiv) are in accordance with these predictions, with increasing monoiodide/diiodide ratios in the order **1a** < **1b** < **1c**. Interestingly, the second experimental deprotonation site also corresponds to the second CH acidic site (Table 3, entries 1–3). It is also important to note that, in the absence of other substituent able to coordinate a metal (either of the base or of the metallated species), the azole nitrogen can play this role and direct the reaction to the 4 and 2′ position.

When a methoxy group is introduced at the 4 position of the phenyl ring (substrate **1d**), the neighbouring (*ortho* and *para*) sites are acidified by its inductive effect whereas the acidity at the 4 position of the 1,2,3-triazole ring is lowered due to electron-donation. What is thus expected is a first metallation at C4 and further reactions at C2′ or C3′. Experimentally, mixtures were obtained. If low differences between the different CH acidities can be advanced to explain these mixtures, one has also to take into account the contribution of the coordinating ability of the methoxy group (Table 3, entry 4).

The calculations performed on the chloro derivative **1e** show that the halogen exhibits a strong acidifying effect; not only its *ortho* hydrogens, but also those at the *meta* and *para* positions are significantly acidified.[33] In this case, the experimental results contrast with an expected reaction at C2′; indeed, if the 4,2′-diiodide **3e** is formed, the main product **3′e** results from a second proton abstraction at C6′, which is far from the most acidic site.

The reason why a major deproto-metallation is not observed at C2′, in spite of several pK_a units in favour of this site, could be steric hindrance; a similar result but in the case of 1-(2-chloropyridin-4-yl)pyrazole has previously been reported.[10] Again, the lone pairs of the chloro group or the azole ring can be involved in metal complexation with impact on the regioselectivity (notably through CH acidity changes).

Conclusions

For the first time, 2-aryl-1,2,3-triazoles have been deproto-metallated. These functionalizations were achieved using mixed lithium–zinc bases, which are compatible with sensitive substrates and do not lead to subsequent ring opening as observed with more polar reagents (Scheme 1, right). Once again, mixed alkali metal–metal bases proved efficient for the functionalization of sensitive substrates, as recently observed in pyrazole series.[10,34] The iodo derivatives thus generated could be elaborated, for example by Suzuki cross-coupling as shown recently in the pyrazole series.[10]

The CH acidities of the substrates in THF solution, which were calculated using a continuum solvation model, were used to rationalize the outcome of the reactions.

Experimental

Syntheses: general methods

Metallation reactions were performed under an argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40–63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin-Elmer Spectrum 100 spectrometer. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak, ^{13}C chemical shifts are relative to the central peak of the solvent signal,[35] and coupling constants (J) are given in Hz. Mass spectra (HRMS) measurements were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes using either a Waters Q-TOF 2 or a Bruker micrOTOF Q II instrument in positive electrospray CI mode.

2-Phenyl-2*H*-[1,2,3]triazole (1a) was prepared from phenylhydrazine hydrochloride using a described procedure.[19] Yield: 82%. Colourless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35 (m, 1H), 7.49 (m, 2H), 7.81 (s, 2H), 8.09 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) 119.1 (2C), 127.7, 129.4 (2C), 135.6 (2C), 140.0. These values are consistent with those reported in the literature.[20]

2-(4-Methylphenyl)-2*H*-[1,2,3]triazole (1b) was prepared from 4-methyl-phenylhydrazine hydrochloride using a described procedure.[19] Yield: 50%. Brown solid (mp = 55 °C). This value is consistent with that reported in the literature.[36] IR (ATR): 3131, 3044, 2923, 1514, 1411, 1381, 1259, 1151, 961, 951, 817 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) 2.40 (s, 3H), 7.28 (d, 2H, J = 8.2), 7.79 (s, 2H), 7.95 (d, 2H, J = 8.2). ^{13}C NMR ($CDCl_3$, 75 MHz) 21.2, 119.0 (2C), 129.9 (2C), 135.3 (2C), 137.6, 137.9.

2-(4-Isopropylphenyl)-2*H*-[1,2,3]triazole (1c) was prepared from 4-isopropyl-phenylhydrazine hydrochloride using a described procedure.[19] Yield: 61%. Colourless liquid. IR (ATR): 2961, 2872, 1516, 1411, 1381, 1260, 1060, 962, 950, 835, 818 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) 1.28 (d, 6H, J = 6.9), 2.97 (m, 1H), 7.34 (d, 2H, J = 8.7), 7.79 (s, 2H), 7.98 (d, 2H, J = 8.7). ^{13}C NMR ($CDCl_3$, 75 MHz) 24.1 (2C), 33.9, 119.1 (2C), 127.4 (2C), 135.4 (2C), 138.0, 148.6. HRMS (ESI): calcd for $C_{11}H_{14}N_3$ $[M + H]^+$ 188.1188, found 188.1190.

2-(4-Methoxyphenyl)-2*H*-[1,2,3]triazole (1d) was prepared from 4-methoxy-phenylhydrazine hydrochloride using a described procedure.[19] Yield: 64%. Colourless liquid. IR (ATR): 2961, 2839, 1509, 1412, 1246, 1168, 1088, 1028, 952, 829 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) 3.86 (s, 3H), 6.99 (d, 2H, J = 9.2), 7.77 (s, 2H), 7.98 (d, 2H, J = 9.2). ^{13}C NMR ($CDCl_3$, 75 MHz) 55.7, 114.5 (2C), 120.5 (2C), 133.9, 135.2 (2C), 159.1. HRMS (ESI): calcd for $C_9H_{10}N_3O$ $[M + H]^+$ 176.0824, found 176.0824.

2-(3-Chlorophenyl)-2*H*-[1,2,3]triazole (1e) was prepared from 3-chloro-phenylhydrazine hydrochloride using a described procedure.[19] Yield: 88%. White solid (mp = 45 °C). IR (ATR): 3099, 3079, 1595, 1487, 1409, 1374, 1263, 1105, 961, 952, 822, 778 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.33 (ddd, 1H, J = 1.1, 2.0 and 8.0 Hz), 7.42 (dd, 1H, J = 8.0 and 8.1 Hz), 7.83 (s, 2H), 7.99 (ddd, 1H, J = 1.1, 2.1 and 8.1 Hz), 8.13 (dd, 1H, J = 2.0 and 2.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) 117.1, 119.4, 127.7, 130.5, 135.3, 136.1 (2C), 140.8. HRMS (ESI): calcd for $C_8H_7{}^{35}ClN_3$ $[M + H]^+$ 180.03285, found 180.0329.

Typical procedure for the deproto-metallation followed by trapping with electrophiles. To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (5 mL) was added BuLi (about 1.6 m hexanes solution, 1.5 mmol). After 15 min at 0 °C, $ZnCl_2$·TMEDA (0.125 g, 0.5 mmol) was added and the mixture was stirred for 15 min at this temperature before the introduction of the substrate (1.0 mmol). After 2 h at room temperature, a solution of I_2 (0.37 g, 1.5 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4-Iodo-2-phenyl-2*H*-[1,2,3]triazole (2a). Yellow solid (mp = 82 °C). IR (ATR): 3123, 3063, 1598, 1497, 1437, 1371, 1354, 1129, 980, 961, 755 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) 7.38 (m, 1H), 7.50 (m, 2H), 7.86 (s, 1H), 8.04 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) 91.6, 118.8 (2C), 128.2, 129.5 (2C), 139.5, 142.5. HRMS (ESI): calcd for $C_8H_7IN_3$ $[M + H]^+$ 271.9685, found 271.9686.

Phenyl-(2-phenyl-2*H*-[1,2,3]-triazol-4-yl)methanone (2a′). Brown solid (mp = 158 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.41–7.69 (m, 6H), 8.17 (m, 2H), 8.37 (m, 2H), 8.42 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 119.6 (2C), 128.6 (2C), 128.7, 129.6 (2C), 130.5 (2C), 133.6, 136.6, 138.8, 139.5, 147.5, 185.7. These values are consistent with those reported in the literature.[37]

4-Iodo-2-(4-methylphenyl)-2*H*-[1,2,3]triazole (2b). Yellow solid (mp = 78 °C). IR (ATR): 3124, 3035, 2919, 2857, 1511,

1440, 1377, 1356, 1128, 980, 960, 815 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 2.40 (s, 3H), 7.27 (d, 2H, J = 8.6), 7.82 (s, 1H), 7.91 (d, 2H, J = 8.6). ^{13}C NMR ($CDCl_3$, 75 MHz) 21.2, 91.2, 118.8 (2C), 130.0 (2C), 140.8, 141.5, 142.3. HRMS (ESI): calcd for $C_9H_9IN_3$ $[M + H]^+$ 285.9841, found 285.9841.

4-Iodo-2-(4-isopropylphenyl)-2*H*-[1,2,3]triazole (2c). Yellow liquid. IR (ATR): 2959, 2926, 2870, 1513, 1445, 1420, 1374, 1356, 1128, 1052, 980, 960, 834 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 1.28 (d, 6H, J = 6.9), 2.96 (m, 1H), 7.32 (d, 2H, J = 8.6), 7.82 (s, 1H), 7.94 (d, 2H, J = 8.6). ^{13}C NMR ($CDCl_3$, 75 MHz) 24.1 (2C), 33.9, 91.2, 118.8 (2C), 127.4 (2C), 137.6, 142.3, 149.1. HRMS (ESI): calcd for $C_{11}H_{13}IN_3$ $[M + H]^+$ 314.0154, found 314.0150.

2-(3-Chlorophenyl)-4-iodo-2*H*-[1,2,3]triazole (2e). Yellow solid (mp = 98 °C). IR (ATR): 3132, 3074, 2921, 2851, 1566, 1455, 1414, 1352, 1261, 1219, 1126, 1023, 980, 962, 840 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 7.34 (ddd, 1H, J = 1.2, 1.9 and 8.0), 7.41 (dd, 1H, J = 8.0 and 8.0), 7.85 (s, 1H), 7.94 (ddd, 1H, J = 1.2, 2.1 and 8.0), 8.09 (dd, 1H, J = 1.9 and 2.1). ^{13}C NMR ($CDCl_3$, 75 MHz) 92.3, 116.8, 119.1, 128.2, 130.6, 135.4, 140.2, 143.0. HRMS (ESI): calcd for $C_8H_6{}^{35}ClIN_3$ $[M + H]^+$ 305.9295, found 305.9295.

4-Iodo-2-(2-iodophenyl)-2*H*-[1,2,3]triazole (3a). Yellow liquid. IR (ATR): 3052, 2930, 1501, 1479, 1437, 1382, 1264, 1023, 981, 960, 843 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 7.20 (m, 1H), 7.48 (m, 2H), 7.92 (s, 1H), 8.00 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 91.6, 92.6, 127.8, 129.1, 131.3, 140.7, 141.2, 142.7. HRMS (ESI): calcd for $C_8H_6I_2N_3$ $[M + H]^+$ 397.8651, found 397.8650.

4-Iodo-2-(2-iodo-4-methylphenyl)-2*H*-[1,2,3]triazole (3b). Yellow solid (mp = 108 °C). IR (ATR): 3132, 2922, 2853, 2431, 1493, 1431, 1260, 1125, 1027, 979, 962, 839, 821 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 2.39 (s, 3H), 7.26 (m, 1H), 7.34 (d, 1H, J = 8.1), 7.81 (m, 1H), 7.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 20.9, 91.3, 92.5, 127.3, 129.7, 140.5, 140.8, 141.9, 142.5. HRMS (ESI): calcd for $C_9H_8I_2N_3$ $[M + H]^+$ 411.8808, found 411.8811.

4-Iodo-2-(2-iodo-4-isopropylphenyl)-2*H*-[1,2,3]triazole (3c). Yellow liquid. IR (ATR): 3003, 2960, 2932, 1709, 1421, 1359, 1221, 1092, 982, 962, 902 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 1.27 (d, 6H, J = 6.9), 2.94 (m, 1H), 7.31 (dd, 1H, J = 1.8 and 8.1), 7.37 (d, 1H, J = 8.1), 7.82 (d, 1H, J = 1.8), 7.90 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 23.9 (2C), 33.8, 91.3, 92.8, 127.2, 127.5, 138.5, 140.6, 142.5, 152.8. HRMS (ESI): calcd for $C_{11}H_{12}I_2N_3$ $[M + H]^+$ 439.9121, found 439.9105.

4-Iodo-2-(2-iodo-4-methoxyphenyl)-2*H*-[1,2,3]triazole (3d). Yellow solid (mp = 58 °C). IR (ATR): 2968, 2935, 2839, 1593, 1569, 1495, 1439, 1295, 1264, 1239, 1227, 1029, 1018, 980, 960, 841 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 3.85 (s, 3H), 6.97 (dd, 1H, J = 2.7 and 8.8), 7.35 (d, 1H, J = 8.8), 7.46 (d, 1H, J = 2.7), 7.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 56.0, 91.2, 93.7, 114.6, 125.1, 128.3, 136.3, 142.4, 160.7. HRMS (ESI): calcd for $C_9H_7I_2NaN_3O$ $[M + Na]^+$ 449.8576, found 449.8570.

4-Iodo-2-(3-iodo-4-methoxyphenyl)-2*H*-[1,2,3]triazole (3′d). Yellow solid (mp = 140 °C). IR (ATR): 2939, 2841, 1493, 1440, 1269, 1245, 1043, 1017, 981, 965, 809 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 3.93 (s, 3H), 6.88 (d, 1H, J = 8.9), 7.81 (s, 1H), 7.98 (dd, 1H, J = 2.6 and 8.9), 8.47 (d, 1H, J = 2.6). ^{13}C NMR ($CDCl_3$, 75 MHz) 56.9, 85.9, 91.4, 110.6, 120.0, 129.9, 133.9, 142.4, 158.1. HRMS (ESI): calcd for $C_9H_8I_2N_3O$ $[M + H]^+$ 427.8757, found 427.8748.

2-(3-Chloro-2-iodophenyl)-4-iodo-2*H*-[1,2,3]triazole (3e). Yellow solid (mp = 84 °C). IR (ATR): 2924, 2849, 1594, 1483, 1455, 1432, 1371, 1353, 1128, 982, 963, 779 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 7.31 (dd, 1H, J = 1.5 and 7.9), 7.42 (dd, 1H, J = 7.9 and 8.0), 7.61 (dd, 1H, J = 1.5 and 8.0), 7.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 91.8, 99.6, 126.0, 129.7, 130.7, 141.0, 142.8, 145.0. HRMS (ESI): calcd for $C_8H_5{}^{35}ClI_2N_3$ $[M + H]^+$ 431.8261, found 431.8262.

2-(5-Chloro-2-iodophenyl)-4-iodo-2*H*-[1,2,3]triazole (3′e). Yellow solid (mp = 102 °C). IR (ATR): 3127, 3086, 2926, 1577, 1561, 1472, 1442, 1414, 1352, 1099, 1019, 981, 961, 874, 815 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 7.19 (dd, 1H, J = 2.4 and 8.5), 7.51 (d, 1H, J = 2.4), 7.91 (d, 1H, J = 8.5), 7.92 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 89.2, 82.2, 127.8, 131.3, 135.1, 141.5, 143.0, 143.3. HRMS (ESI): calcd for $C_8H_5{}^{35}ClI_2N_3$ $[M + H]^+$ 431.8261, found 431.8270.

2-(2-Iodo-4-methylphenyl)-2*H*-[1,2,3]triazole (4b). Brown solid (mp = 124 °C). IR (ATR): 3139, 2956, 2922, 1514, 1498, 1411, 1251, 1150, 1024, 962, 951, 819 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 2.40 (s, 3H), 7.27 (m, 1H), 7.35 (d, 1H, J = 8.1), 7.82 (m, 1H), 7.87 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) 20.8, 92.8, 127.4, 129.7, 135.5 (2C), 140.8, 141.0, 141.5. HRMS (ESI): calcd for $C_9H_9IN_3$ $[M + H]^+$ 285.9841, found 285.9838.

2-(2-Iodo-4-methoxyphenyl)-2*H*-[1,2,3]triazole (4d). Orange solid (mp = 92 °C) which rapidly decomposes by loss of iodine. ^1H NMR ($CDCl_3$, 300 MHz) 3.86 (s, 3H), 6.84 (dd, 1H, J = 2.7 and 8.8), 7.36 (d, 1H, J = 8.8), 7.48 (d, 1H, J = 2.7), 7.86 (s, 2H).

2-(2,5-Diiodo-4-methoxyphenyl)-4-iodo-2*H*-[1,2,3]triazole (5d). Yellow liquid. IR (ATR): 3120, 2968, 2936, 2841, 1485, 1437, 1333, 1241, 1043, 1019, 981, 961, 838, 820 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) 3.95 (s, 3H), 7.28 (s, 1H), 7.82 (s, 1H), 7.89 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) 57.2, 85.3, 91.6, 92.9, 121.2, 137.1, 137.5, 142.7, 159.5. HRMS (ESI): calcd for $C_9H_6I_3NaN_3O$ $[M + Na]^+$ 575.7543, found 575.7545.

Crystallography

Single crystals suitable for X-ray diffraction were grown after slow evaporation of solutions of **2a**, **2e**, **3b**, **3d**, **3′d**, **3e**, **3′e** and **4b** in dichloromethane at room temperature.

The samples were studied with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). X-ray diffraction data were collected at T = 150(2) K using APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,[38] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[39] with the aid of the WINGX program.[40] All non-hydrogen atoms were refined with anisotropic thermal parameters. H atoms were finally included in their calculated positions. Except *N*-linked hydrogen that was introduced in the structural model through Fourier difference maps analysis, H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).[41]

Crystal data for 2a. $C_8H_6IN_3$, M_r = 271.06, orthorhombic, $Pc2_1n$, a = 4.3176(3), b = 13.3505(10), c = 15.2661(12) Å, V =

879.97(11) Å^3, $Z = 4$, $\rho_c = 2.046$ g cm^{-3}, $\mu = 3.584$ mm^{-1}. A final refinement on F^2 with 1992 unique intensities and 109 parameters converged at w$R(F^2) = 0.0398$ ($R(F) = 0.0183$) for 1792 observed reflections with $I > 2\sigma(I)$.

Crystal data for 2e. $C_8H_5ClIN_3$, $M_r = 305.50$, orthorhombic, $Pc2_1n$, $a = 4.2056(5)$, $b = 13.2551(18)$, $c = 17.169(2)$ Å, $V = 957.1(2)$ Å^3, $Z = 4$, $\rho_c = 2.12$ g cm^{-3}, $\mu = 3.578$ mm^{-1}. A final refinement on F^2 with 2164 unique intensities and 118 parameters converged at w$R(F^2) = 0.0418$ ($R(F) = 0.0183$) for 2059 observed reflections with $I > 2\sigma(I)$.

Crystal data for 3b. $C_9H_7I_2N_3$, $M_r = 410.98$, monoclinic, $P2_1/c$, $a = 10.3473(15)$, $b = 7.1028(8)$, $c = 15.555(2)$ Å, $\beta = 104.138(6)°$, $V = 1108.6(2)$ Å^3, $Z = 4$, $\rho_c = 2.462$ g cm^{-3}, $\mu = 5.638$ mm^{-1}. A final refinement on F^2 with 2544 unique intensities and 128 parameters converged at w$R(F^2) = 0.0588$ ($R(F) = 0.0249$) for 2320 observed reflections with $I > 2\sigma(I)$.

Crystal data for 3d. $2(C_9H_7I_2N_3O)$, $M_r = 853.95$, triclinic, $P\bar{1}$, $a = 7.7817(6)$, $b = 10.5301(8)$, $c = 14.2726(11)$ Å, $\alpha = 79.833(4)$, $\beta = 89.092(4)$, $\gamma = 80.124(4)°$, $V = 1133.98(15)$ Å^3, $Z = 2$, $\rho_c = 2.501$ g cm^{-3}, $\mu = 5.524$ mm^{-1}. A final refinement on F^2 with 5165 unique intensities and 273 parameters converged at w$R(F^2) = 0.0895$ ($R(F) = 0.0374$) for 4179 observed reflections with $I > 2\sigma(I)$.

Crystal data for 3′d. $C_9H_7I_2N_3O$, $M_r = 426.98$, orthorhombic, $Pc2_1n$, $a = 4.1304(2)$, $b = 12.9948(5)$, $c = 21.5358(9)$ Å, $V = 1155.91(9)$ Å^3, $Z = 4$, $\rho_c = 2.454$ g cm^{-3}, $\mu = 5.419$ mm^{-1}. A final refinement on F^2 with 2314 unique intensities and 137 parameters converged at w$R(F^2) = 0.0498$ ($R(F) = 0.0228$) for 2273 observed reflections with $I > 2\sigma(I)$.

Crystal data for 3e. $C_8H_4ClI_2N_3$, $M_r = 431.39$, orthorhombic, $P2_1cn$, $a = 7.8011(19)$, $b = 9.106(2)$, $c = 15.558(4)$ Å, $V = 1105.2(5)$ Å^3, $Z = 4$, $\rho_c = 2.593$ g cm^{-3}, $\mu = 5.896$ mm^{-1}. A final refinement on F^2 with 2515 unique intensities and 127 parameters converged at w$R(F^2) = 0.0386$ ($R(F) = 0.0178$) for 2480 observed reflections with $I > 2\sigma(I)$.

Crystal data for 3′e. $C_8H_4ClI_2N_3$, $M_r = 431.39$, monoclinic, $P2_1/c$, $a = 10.8653(4)$, $b = 7.7070(2)$, $c = 13.2464(5)$ Å, $\beta = 93.5294(18)°$, $V = 1107.13(7)$ Å^3, $Z = 4$, $\rho_c = 2.588$ g cm^{-3}, $\mu = 5.886$ mm^{-1}. A final refinement on F^2 with 2508 unique intensities and 127 parameters converged at w$R(F^2) = 0.056$ ($R(F) = 0.0224$) for 2368 observed reflections with $I > 2\sigma(I)$.

Crystal data for 4b. $C_9H_8IN_3$, $M_r = 285.08$, monoclinic, $P2_1/n$, $a = 7.993(2)$, $b = 14.366(4)$, $c = 8.736(2)$ Å, $\beta = 94.686(13)°$, $V = 999.8(4)$ Å^3, $Z = 4$, $\rho_c = 1.894$ g cm^{-3}, $\mu = 3.160$ mm^{-1}. A final refinement on F^2 with 2254 unique intensities and 119 parameters converged at w$R(F^2) = 0.0783$ ($R(F) = 0.0337$) for 2096 observed reflections with $I > 2\sigma(I)$.

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