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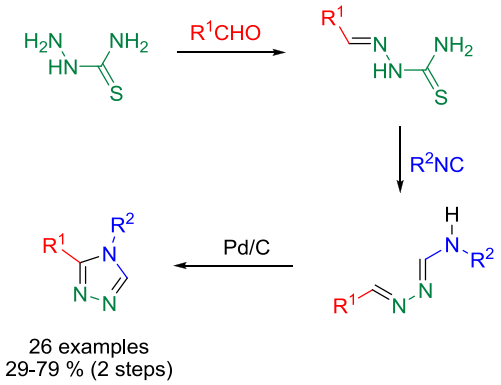

Synthesis of 1,2,4-triazoles employing isocyanides

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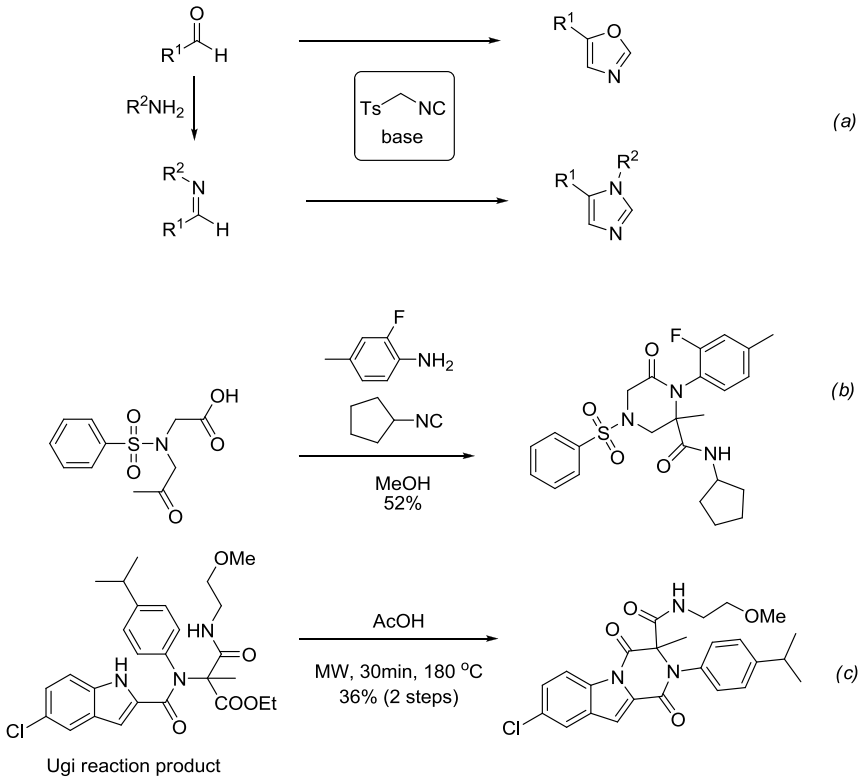
Abstract: a conceptually new, two-step synthesis of medicinally important 1,2,4-triazoles from isocyanides and thiosemicarbazones was developed. The method is based on the recently discovered TMSCl-promoted reaction of isocyanides that yields rare N^1,N^3-disubstututed formamidrazones.

Keywords: isocyanides, TMSCl-promoted reaction, formamidrazones, 1,2,4-triazoles, convergent synthesis, dehydrogenation

1. Introduction

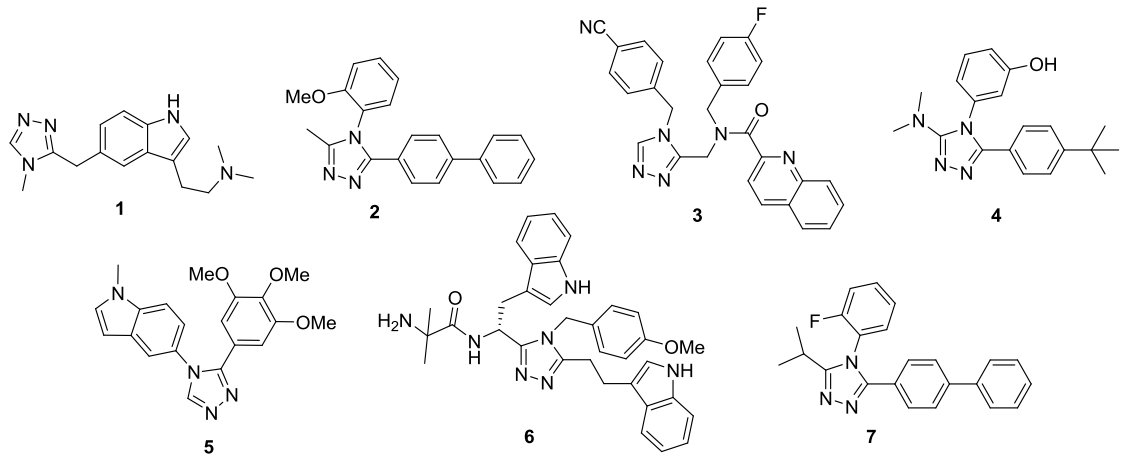
The synthetic utility of isocyanides extends far beyond the preparation of α-acyloxy and α-acylaminocarboxamides via the 'classical' Passerini[1] and Ugi[2] reactions, respectively, as this reagent class continues to prove instrumental in *de novo* heterocycle construction. The unique reactivity of α-acidic *p*-toluenesulfonylmethylisocyanide (TosMIC) enabled the van Leusen imidazole[3] and oxazole[4] syntheses; numerous cases of successful use of bifunctional reagents[5] and post-condensational modifications[6] in conjunction with the Ugi reaction clearly attest to the power of isocyanide chemistry to reach into new areas of heterocyclic chemical space, aromatic and saturated alike (Scheme 1).

Scheme 1. Isocyanides in heterocycle synthesis: (*a*) van Leusen azole syntheses; examples of (*b*) a bifunctional ketocarboxylic acid use in the Ugi reaction and (*c*) a post-Ugi modification leading to a novel heterocyclic framework.



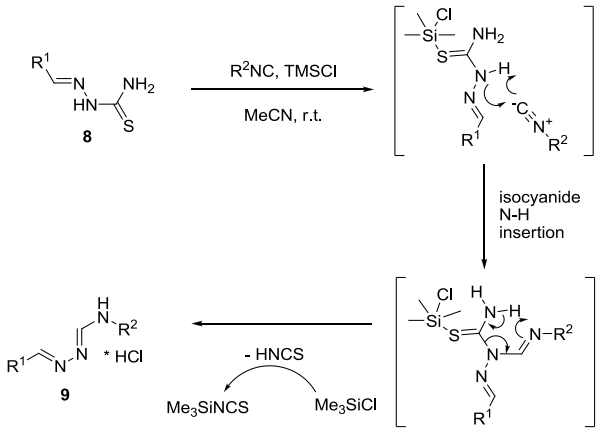
1,2,4-Triazoles constitute an important class of heterocycles and have been reported as key to a number of pharmacologically active compounds: potent 5HT antagonist **1**,[7] arginine vasopressin V_{1A} receptor antagonist **2**,[8] Ras farnesyl transferase inhibitor **3**,[9] δ opioid receptor antagonist **4**,[10] tubulin polymerization inhibitor **5**,[11] high-affinity ligand to the human ghrelin receptor **6**[12] and glycine transporter 1 inhibitor **7**[13] are only a few examples illustrating the privileged character[14] of the 1,2,4-triazole core for the drug design (Figure 1).

Figure 1. Examples of pharmacologically active 1,2,4-triazoles.



Recently, we described a new reaction of isocyanides with aldehyde thiosemicarbazones **8** that yields rare N^1,N^3-disubstituted formamidrazone hydrochlorides **9**.[15] The reaction is promoted by chlorotrimethylsilane (TMSCl) and is thought to proceed via isocyanide N-H insertion followed by the elimination of isothiocyanic acid (Scheme 2). Given the novelty of this reaction and an intriguing arrangement of potentially reactive electrophilic hydrazone and nucleophilic amidine moieties in **9**, we became interested in identifying the utility of the latter for ring-forming processes.[16] Herein we described the application of isocyanide-derived formamidrazones **9** toward facile preparation of diversely substituted 1,2,4-triazoles.

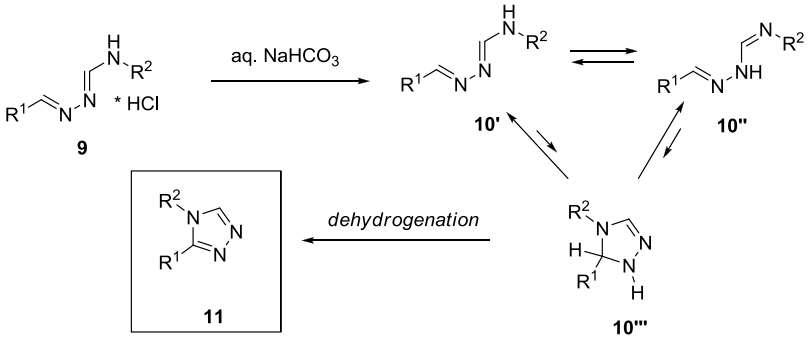
Scheme 2. TMSCl-promoted reaction of isocyanides with aldehyde thiosemicarbazones.[15]



2. Results and discussion

As we reported earlier,[15] in some cases formamidrazone hydrochlorides **9** precipitate from the reaction mixture and can be conveniently isolated and characterized. Their free-base counterparts **10**, however, exist as a mixture of tautomers (presumably, **10'** and **10''**) that complicate their spectroscopic characterization. In principle, ring tautomer **10'''** could also exist in equilibrium with the open-chain tautomers **10'** and **10''** (although only two major tautomers could be detected by ^{1}H NMR spectroscopy). We reasoned that if this was the case, 2,3-dihydro-1,2,4-triazole **10'''** could be aromatized under appropriate dehydrogenation conditions and thus provide a convenient access to 1,2,4-triazoles **11** (Scheme 3).

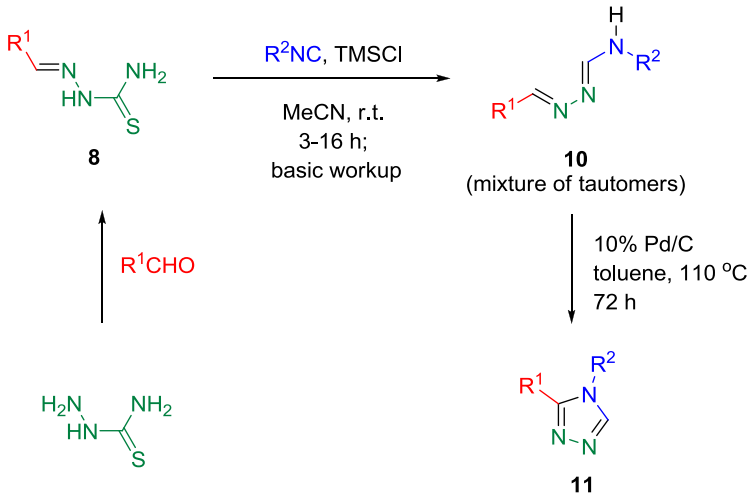
Scheme 3. The rationale for the formation of 1,2,4-triazoles.



A model formamidrazone hydrochloride **9a** (R^1 = 3-chlorophenyl, R^2 = *t*-Bu) that was prepared in high yield (90%) and isolated, in analytically pure form, from the TMSCl-promoted reaction of *t*-BuNC with 3-chlorobenzaldehyde thiosemicarbazone[15] was converted to the free-base formamidrazone (**10a**) and subjected to a number of dehydrogenation conditions. Treatment of **10a** with DDQ[17] in toluene or acetonitrile (at reflux temperatures) as well as with silica gel supported $KMnO_4$[18] (acetonitrile, r.t.) gave a complex mixture of unidentified products. However, a promising result was obtained upon treatment of **10a** with 10% Pd on activated charcoal (toluene, 110 °C).[19] Under these conditions, **10a** underwent a steady (albeit somewhat slow) conversion to a more polar product that was isolated

chromatographically in 72% yield and its identity as the desired 1,2,4-triazole **11a** was established by ^{1}H and ^{13}C NMR spectroscopy, LC MS, and high-resolution mass-spectrometry. In contrast, under the same reaction conditions, hydrochloride **9a** remained unchanged upon extended heating (7 days). This observation appears to be consistent with the formamidrazone hydrochloride's being 'locked' as open-chain tautomer **10'** (as was earlier established by X-ray crystallography),[15] which renders it unavailable for the formation of the postulated ring tautomer **10'''** and subsequent dehydrogenation.

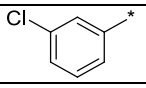
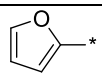
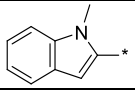
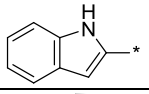
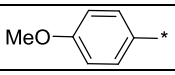
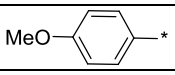
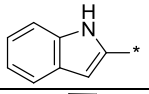
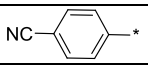
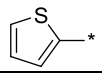
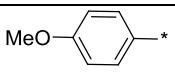
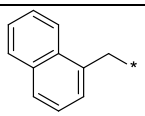
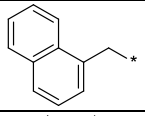
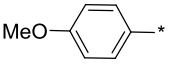
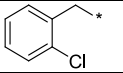
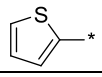
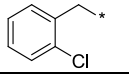
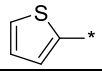
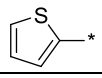
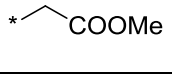
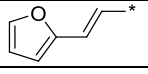
Scheme 4. 1,2,4-Triazole synthesis developed in this work.

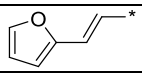
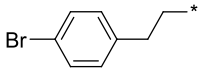
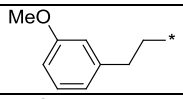
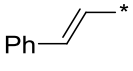
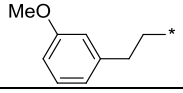
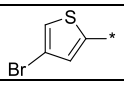
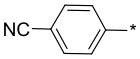
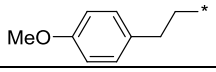
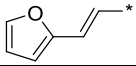
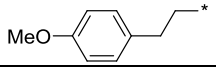
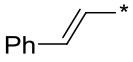
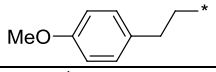
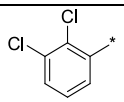
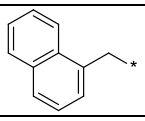
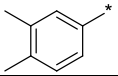


The newly established synthetic approach was applied to a diverse range of free-base formamidrazones **10b-z** that were also prepared via the TMSCl-promoted reaction of thiosemicarbazones **8** with aliphatic isocyanides, followed by basic work-up of the reaction mixture. In principle, the crude formamidrazones could be used in the dehydrogenative cyclization step directly (Scheme 4). However, better yields and easier purification of the target 1,2,4-triazoles were obtained from formamidrazones that were briefly fractionated by silica gel chromatography to achieve at least 80% purity (as judged by LC MS analysis). The isolated yields of the 1,2,4-triazoles **11b-z** from thiosemicarbazones **8**, were fair to excellent (Table 1).[20] Notably, when we repeated the synthesis of **11a** without the isolation of **9a** and

proceeded with the basic workup of the reaction mixture and fractionation of the free-base product, the yield of **11a** was even slightly higher (76%) than that obtained via isolation of the formamidrazone hydrochloride by filtration (possibly due to a partial solubility of **9a** in acetonitrile).

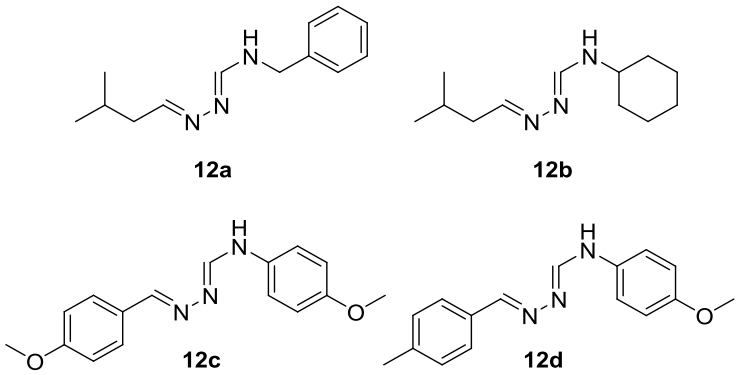
Table 1. 3,4-Disubstituted 1,2,4-triazoles **11** synthesized in this work.

Compound	R^1	R^2	*m/z* of **10** by LC MS ($[M+H]^+$)	Yield of **11** (%)
11a		*t*-Bu	194.4	76 (72)[a]
11b		*t*-Bu	238.4	69
11c		cyclohexyl	283.5	64
11d		*t*-Bu	243.5	54
11e		cyclohexyl	260.5	78
11f		*t*-Bu	234.4	70
11g		cyclohexyl	269.2	61
11h		*t*-Bu	229.5	58
11i		*t*-Bu	210.5	38
11j			318.5	73
11k			294.5	63
11l			302.5	79
11m			278.6	61
11n		cyclohexyl	236.5	52
11o			226.5	29
11p		*t*-Bu	220.5	70

11q		cyclohexyl	246.6	71
11r			336.6	47
11s			288.6	54
11t			308.7	66
11u		cyclohexyl	314.3	33
11v			307.7	72
11w			298.6	74
11x			308.7	77
11y			357.6	38
11z		*t*-Bu	232.4	63

[a] Yield in parentheses obtained with the isolation of formamidrazone **9a** by filtration, prior to its conversion to free-base **10a**.

Figure 2. Examples of formamidrazones that failed to give 1,2,4-triazoles.



This conceptually new methodology for constructing the 3,4-disubstituted 1,2,4-triazoles complements the earlier described synthetic strategies[21] and is suitable for convenient synthesis of diverse representatives of this medicinally important chemical class (for example, compound **11y** was reported as a potent P2X7 ion channel blocker).[22] 1,2,4-

Triazoles with a wide range of 3-(hetero)aromatic as well as stiryl-type substituents are easily accessible by the new synthetic route. The latter, however, does not appear to be applicable to the preparation of 3-alkyl- and/or 4-aryl-substituted 1,2,4-triazoles as free-base formamidrazones **12a-d** (reported by us earlier[15]) failed to give the anticipated products on treatment with Pd/C (Figure 2).[23]

3. Conclusion

In conclusion, we have described a conceptually new preparation of 1,2,4-triazoles and the first practical application of the rare, isocyanide-derived N^1,N^3-disubstituted formamidrazones in heterocycle synthesis. Our convergent and technically simple approach significantly extends the modern arsenal of methods to prepare this important class of heterocyclic compounds.

4. Experimental Section.

4.1 General

Dry acetonitrile (MeCN) was obtained by passing commercially available predried, oxygen-free formulations through activated alumina columns. All other compounds were used as received from the suppliers. The crude reaction mixtures were concentrated under reduced pressure by removing organic solvents on rotary evaporator. Column chromatography was performed using silica gel 60 (particle size 0.040-0.063 mm, 230-400 mesh ASTM). Analytical thin-layer chromatography (TLC) was performed with silica gel 60 F254 aluminum sheets. Chemical shifts for nuclear magnetic resonance (NMR) spectra were reported in parts per million (ppm, δ) using the residual solvent peaks as internal standard. Splitting patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), doublet of doublet (dd), triplet of triplet (tt), and quartet of doublet (qd). High resolution mass spectra (HRMS) were acquired using a Fourier Transform Ion Cyclotron Resonance spectrometer fitted with an electrospray source and operating in positive ion mode.

4.2 Typical procedure: Synthesis of 1,2,4-triazoles 11.

A stirred suspension (solution) of a thiosemicarbazone (1 mmol) in dry acetonitrile (10 mL) was treated with TMSCl (1 mmol) and stirred for 10 min at r.t. An isocyanide (1.1 mmol) was added, the reaction flask was purged with argon and the reaction mixture was stirred at r.t. for 3-16 h, until TLC analysis indicated a complete disappearance of the starting thiosemicarbazone. The reaction mixture was partitioned between EtOAc and sat. aq. $NaHCO_3$, the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to provide the crude formamidrazone **10**. The latter was briefly fractionated on a short silica gel column (using an appropriate mixture of EtOAc in hexanes or MeOH in DCM) to provide >80% pure formamidrazone (as judged by LC MS analysis). The latter was combined, in a sealed tube, with 10% palladium on activated charcoal (equal amount wt/wt) in toluene (5 mL) and the resulting mixture was heated, under vigorous stirring, at 110°C for 72 h. The cooled reaction mixture was diluted with an equal volume of methanol and sonicated for 3 min. It was then filtered through a plug of Celite and the latter was washed again with copious amounts of methanol. The combined filtrate and washings were concentrated *in vacuo* to provide the crude product. The latter was purified by chromatography on silica gel using an appropriate gradient of MeOH in CH_2Cl_2 to provide the analytically pure 1,2,4-triazole **11**.

4.3 Analytical data for the obtained compounds.

*4.3.1 4-tert-Butyl-3-(3-chlorophenyl)-4H-1,2,4-triazole (**11a**)*. Pale yellow solid, mp = 123-126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.47 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.45 – 7.42 (m, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.33 (dd, *J* = 7.8, 1.0 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9, 134.2, 131.9, 130.7, 130.1, 129.5, 128.8, 128.1, 57.6, 31.0; HRMS *m/z* [M+Na^+] calcd for $C_{12}H_{14}{}^{35}ClN_3Na$ 258.0768, found 258.0750.

*4.3.2 4-tert-Butyl-3-(furan-2-yl)-4H-1,2,4-triazole (**11b**).* Pale yellow solid, mp = 108-110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.54 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.81 (dd, *J* = 3.4, 0.8 Hz, 1H), 6.49 (dd, *J* = 3.4, 1.9 Hz, 1H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 143.5, 142.1, 141.6, 113. 9, 111.5, 57.4, 30.0; HRMS *m/z* [M+Na^+] calcd for $C_{10}H_{13}N_3NaO$ 214.0951, found 214.0941.

*4.3.3 2-(4-Cyclohexyl-4H-1,2,4-triazol-3-yl)-1-methyl-1H-indole (**11c**).* Light yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (s, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.70 (s, 1H), 4.25 (tt, *J* = 12.1, 3.7 Hz, 1H), 3.90 (s, 3H), 2.12 – 2.07 (m, 2H), 1.94 – 1.85 (m, 2H), 1.80 – 1.63 (m, 3H), 1.43 – 1.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 138.3, 127.1, 124.9, 123.5, 121.3, 120.4, 110.1, 104.4, 55.4, 34.6, 31.4, 25.4, 24.9; HRMS *m/z* [M+Na^+] calcd for $C_{17}H_{20}N_4Na$ 303.1580, found 303.1583.

*4.3.4 2-(4-tert-Butyl-4H-1,2,4-triazol-3-yl)-1H-indole (**11d**).* Light orange solid, mp = 198-199 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.57 (s, 1H), 8.25 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 1.59 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 142.1, 136.3, 127.6, 124.6, 123.3, 120.8, 120.1, 111.9, 105.8, 57.5, 30.2; HRMS *m/z* [M+H^+] calcd for $C_{14}H_{17}N_4$ 241.1448, found 241.1448.

*4.3.5 4-Cyclohexyl-3-(4-methoxyphenyl)-4H-1,2,4-triazole (**11e**).* Pale yellow solid, mp = 96-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 3.92 (tt, *J* = 12.0, 3.7 Hz, 1H), 3.79 (s, 3H), 2.01 – 1.93 (m, 2H), 1.84 – 1.76 (m, 2H), 1.70 – 1.49 (m, 3H), 1.31 – 1.09 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.7, 153.2, 140.9, 130.1, 119.3, 114.2, 55.2, 54.9, 34.3, 25.2, 24.7; HRMS *m/z* [M+H^+] calcd for $C_{15}H_{20}N_3O$ 258.1601, found 258.1595.

*4.3.6 4-tert-Butyl-3-(4-methoxyphenyl)-4H-1,2,4-triazole (**11f**).* White solid, mp = 173-175 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 153.5, 141.6, 131.8, 122.0, 113.5, 57.0, 55.2, 30.8; HRMS *m/z* [M+Na^+] calcd for $C_{13}H_{17}N_3NaO$ 254.1264, found 254.1261.

*4.3.7 2-(4-Cyclohexyl-4H-1,2,4-triazol-3-yl)-1H-indole (**11g**).* Brown solid, mp = 223-225 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.20 (s, 1H), 8.35 (s, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.79 (s, 1H), 4.50 (tt, *J* = 11.9, 3.5 Hz, 1H), 2.33 – 2.27 (m, 2H), 2.05 – 1.98 (m, 2H), 1.97 – 1.83 (m, 1H), 1.77 – 1.67 (m, 2H), 1.64 – 1.49 (m, 2H), 1.41 – 1.27 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 141.2, 136.8, 128.0, 123.8, 123.8, 120.9, 120.3, 112.2, 101.5, 55.7, 34.0, 25.5, 25.0; HRMS *m/z* [M+H^+] calcd for $C_{16}H_{19}N_4$ 267.1604, found 267.1604.

*4.3.8 4-(4-tert-Butyl-4H-1,2,4-triazol-3-yl)benzonitrile (**11h**).* Pale yellow solid, mp = 247-250 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.75 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 142.2, 135.1, 131.9, 131.4, 117.8, 114.0, 57.6, 31.1; HRMS *m/z* [M+Na^+] calcd for $C_{13}H_{14}N_4Na$ 249.1111, found 249.1109.

*4.3.9 4-tert-Butyl-3-(thiophen-2-yl)-4H-1,2,4-triazole (**11i**).* Pale yellow solid, mp = 99-101 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (s, 1H), 7.53 (d, *J* =5.1 Hz, 1H), 7.31 (d, *J* = 3.5 Hz, 1H), 7.13 (dd, *J* = 5.1, 3.5 Hz, 1H), 1.57 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.7, 142.5, 131.8, 129.2, 128.0, 127.0, 58.56, 30.7; HRMS *m/z* [M+Na^+] calcd for $C_{10}H_{13}N_3NaS$ 230.0722, found 230.0720.

*4.3.10 3-(4-Methoxyphenyl)-4-(naphthalen-1-ylmethyl)-4H-1,2,4-triazole (**11j**).* White solid, mp = 136-138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.88 (d, *J* = 7.4 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.64 (d, *J* = 8.3 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.53 – 7.44 (m, 2H),

7.42 – 7.36 (m, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.59 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 154.0, 144.3, 133.6, 130.5, 130.0, 129.9, 129.3, 129.0, 127.0, 126.3, 125.3, 125.0, 121.9, 118.7, 114.3, 55.2, 46.7; HRMS *m/z* [M+H$^+$] calcd for $C_{20}H_{18}N_3O$ 316.1444, found 316.1446.

*4.3.11 4-(Naphthalen-1-ylmethyl)-3-(thiophen-2-yl)-4H-1,2,4-triazole (**11k**).* Yellow solid, mp = 122-123 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.97 – 7.91 (m, 1H), 7.88 (d, *J* = 8.3 Hz, 1H), 7.78 – 7.72 (m, 1H), 7.60 – 7.52 (m, 2H), 7.45 – 7.39 (m, 2H), 7.28 (dd, *J* = 3.7, 1.0 Hz, 1H), 7.06 – 7.01 (m, 2H), 5.74 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.3, 144.6, 133.7, 130.1, 129.8, 129.5, 129.1, 128.6, 127.9, 127.8, 127.4, 127.3, 126.5, 125.5, 125.0, 121.9, 47.0; HRMS *m/z* [M+H$^+$] calcd for $C_{17}H_{14}N_3S$ 292.0903, found 292.0904.

*4.3.12 4-(2-Chlorobenzyl)-3-(4-methoxyphenyl)-4H-1,2,4-triazole (**11l**).* Pale yellow solid, mp = 143-146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.48 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.28 (td, *J* = 7.7, 1.3 Hz, 1H), 7.22 (td, *J* = 7.7, 1.3 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.85 (dd, *J* = 8.0, 1.1 Hz, 1H), 5.26 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.0, 154.2, 144.2, 132.8, 132.8, 130.1, 130.0, 129.9, 128.4, 127.6, 118.6, 114.4, 55.3, 46.5; HRMS *m/z* [M+H$^+$] calcd for $C_{16}H_{15}{}^{35}ClN_3O$ 300.0898, found 300.0893.

*4.3.13 4-(2-Chlorobenzyl)-3-(thiophen-2-yl)-4H-1,2,4-triazole (**11m**).* Pale yellow solid, mp = 89-92 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.46 – 7.40 (m, 2H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.25 – 7.18 (m, 2H), 7.06 (dd, *J* = 5.0, 3.8 Hz, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 5.40 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0, 144.5, 132.6, 132.1, 129.9, 129.9, 128.5, 128.0, 127.8, 127.7, 127.5, 127.0, 46.5; HRMS *m/z* [M+H$^+$] calcd for $C_{13}H_{11}{}^{35}ClN_3S$ 276.0357, found 276.0351.

*4.3.14 4-Cyclohexyl-3-(thiophen-2-yl)-4H-1,2,4-triazole (**11n**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.51 (dd, *J* = 5.1, 1.0 Hz, 1H), 7.41 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.17 (dd, *J* = 5.1, 3.6 Hz, 1H), 4.22 (tt, *J* = 12.0, 3.7 Hz, 1H), 2.17 – 2.11 (m, 2H), 1.97 – 1.88

(m, 2H), 1.82 – 1.74 (m, 1H), 1.66 (qd, *J* = 12.5, 3.3 Hz, 2H), 1.48 – 1.34 (m, 2H), 1.34 – 1.21 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 141.3, 128.3, 128.1, 127.8, 127.7, 55.5, 34.4, 25.4, 24.9; HRMS *m/z* [M+Na^+] calcd for $C_{12}H_{15}N_3NaS$ 256.0879, found 256.0878.

*4.3.15 Methyl 2-(3-(thiophen-2-yl)-4H-1,2,4-triazol-4-yl)acetate (**11o**).* Yellow solid, mp = 120-122 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.53 – 7.51 (m, 1H), 7.36 – 7.34 (m, 1H), 7.20 – 7.13 (m, 1H), 4.88 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 149.1, 144.8, 128.9, 128.4, 127.9, 126.6, 53.25, 46.1; HRMS *m/z* [M+Na^+] calcd for $C_9H_9N_3NaO_2S$ 246.0308, found 246.0306.

*4.3.16 (E)-4-tert-Butyl-3-(2-(furan-2-yl)vinyl)-4H-1,2,4-triazole (**11p**).* Brown solid, mp = 139-140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.50 (d, *J* = 15.6 Hz, 1H), 7.43 (d, *J* = 1.4 Hz, 1H), 6.96 (d, *J* = 15.6 Hz, 1H), 6.49 – 6.42 (m, 2H), 1.68 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.9, 151.8, 143.2, 141.4, 123.1, 112.1, 112.0, 110.8, 56.2, 30.4; HRMS *m/z* [M+Na^+] calcd for $C_{12}H_{15}N_3NaO$ 240.1107, found 240.1106.

*4.3.17 (E)-4-Cyclohexyl-3-(2-(furan-2-yl)vinyl)-4H-1,2,4-triazole (**11q**).* Brown solid, mp = 158-160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.55 (d, *J* = 15.7 Hz, 1H), 7.43 (d, *J* = 1.1 Hz, 1H), 6.66 (d, *J* = 15.7 Hz, 1H), 6.47 (d, *J* = 3.3 Hz, 1H), 6.43 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.96 (tt, *J* = 11.9, 3.7 Hz, 1H), 2.12 – 2.06 (m, 2H), 1.96 – 1.88 (m, 2H), 1.81 – 1.74 (m, 1H), 1.60 (qd, *J* = 12.4, 3.2 Hz, 2H), 1.50 – 1.38 (m, 2H), 1.30 – 1.18 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 151.0, 143.3, 140.5, 123.3, 112.2, 112.0, 107.8, 54.6, 34.0, 25.4, 24.9; HRMS *m/z* [M+H^+] calcd for $C_{14}H_{18}N_3O$ 244.1444, found 244.1442.

*4.3.18 4-(4-Bromophenethyl)-3-(thiophen-2-yl)-4H-1,2,4-triazole (**11r**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s) and 7.90 (s) – total 1H, 7.50 (d, *J* = 5.1 Hz, 1H), 7.41 – 7.33 (m, 2H), 7.30 – 7.23 (m, 1H), 7.15 (dd, *J* = 6.4, 2.2 Hz, 1H), 7.03 (d, *J* = 7.7 Hz) and 6.88 (d, *J* = 7.7 Hz) – total 2H, 4.40 – 4.30 (m, 2H), 3.04 (t, *J* = 7.2 Hz) and 2.99 (t, *J* = 7.2 Hz) – total 2H (biaryl restricted rotation conformers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 144.3, 144.2,

136.1, 135.1, 132.0, 130.3, 129.0, 128.6, 128.4, 128.4, 128.2, 128.1, 127.8, 127.7, 127.3, 127.2, 121.3, 46.6, 46.3, 36.7, 36.1 (biaryl restricted rotation conformers); HRMS *m/z* [M+H$^+$] calcd for $C_{14}H_{13}{}^{79}BrN_3S$ 334.0008, found 334.0006.

*4.3.19 4-(3-Methoxyphenethyl)-3-(thiophen-2-yl)-4H-1,2,4-triazole (**11s**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.49 (d, *J* = 5.1 Hz, 1H), 7.38 (d, *J* = 3.7 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 7.15 (dd, *J* = 5.1, 3.7 Hz, 1H), 6.78 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.54 (s, 1H), 4.35 (t, *J* = 7.1 Hz, 2H), 3.73 (s, 3H), 3.01 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 148.6, 144.3, 137.6, 130.0, 128.4, 128.1, 127.7, 127.4, 120.8, 114.4, 112.6, 55.2, 46.5, 36.7; HRMS *m/z* [M+H$^+$] calcd for $C_{15}H_{16}N_3OS$ 286.1008, found 286.1002.

*4.3.20 (E)-4-(3-Methoxyphenethyl)-3-styryl-4H-1,2,4-triazole (**11t**).* Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.67 (d, *J* = 16.1 Hz, 1H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.39 – 7.28 (m, 3H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.73 (dd, *J* = 8.3, 2.4 Hz, 1H), 6.59 (d, *J* = 7.7 Hz, 1H), 6.55 (s, 1H), 6.51 (d, *J* = 16.1 Hz, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 3.69 (s, 3H), 3.00 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.0, 151.7, 143.4, 137.9, 136.4, 135.6, 130.0, 129.0, 128.7, 127.0, 120.8, 114.5, 112.6, 109.5, 55.1, 45.7, 37.2; HRMS *m/z* [M+H$^+$] calcd for $C_{19}H_{20}N_3O$ 306.1601, found 306.1593.

*4.3.21 3-(4-Bromothiophen-2-yl)-4-cyclohexyl-4H-1,2,4-triazole (**11u**).* Pale yellow solid, mp = 122-124 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.42 (s, 1H), 7.29 (s, 1H), 4.18 (tt, *J* = 11.9, 3.6 Hz, 1H), 2.18 – 2.11 (m, 2H), 2.00 – 1.94 (m, 2H), 1.84 – 1.77 (m, 1H), 1.68 (qd, *J* = 12.5, 3.2 Hz, 2H), 1.51 – 1.37 (m, 2H), 1.35 – 1.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1, 141.6, 130.0, 129.4, 125.5, 110.4, 55.6, 34.3, 25.3, 24.8; HRMS *m/z* [M+H$^+$] calcd for $C_{12}H_{15}{}^{79}BrN_3S$ 312.0164, found 312.0161.

*4.3.22 4-(4-(4-Methoxyphenethyl)-4H-1,2,4-triazol-3-yl)benzonitrile (**11v**).* Yellow solid, mp = 115-118°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.72 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J*

= 8.5 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 4.26 (t, *J* = 6.7 Hz, 2H), 3.76 (s, 3H), 2.92 (t, *J* = 6.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 152.4, 144.6, 132.5, 131.3, 129.5, 129.2, 127.6, 118.0, 114.4, 113.8, 55.2, 47.0, 36.3; HRMS *m/z* [M+Na^+] calcd for $C_{18}H_{16}N_4NaO$ 327.1216, found 327.1209.

*4.3.23 (E)-3-(2-(Furan-2-yl)vinyl)-4-(4-methoxyphenethyl)-4H-1,2,4-triazole (**11w**).* Brown oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.44 (d, *J* = 15.8 Hz, 1H), 7.41 (s, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 6.48 (d, *J* = 15.8 Hz, 1H), 6.45 – 6.39 (m, 2H), 4.14 (t, *J* = 6.8 Hz, 2H), 3.67 (s, 3H), 2.93 (t, *J* = 6.8 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 151.5, 151.4, 143.4, 143.2, 129.5, 128.2, 123.1, 114.2, 112.0, 111.9, 107.3, 55.0, 45.8, 36.1; HRMS *m/z* [M+H^+] calcd for $C_{17}H_{18}N_3O_2$ 296.1394, found 296.1389.

*4.3.24 (E)-4-(4-Methoxyphenethyl)-3-styryl-4H-1,2,4-triazole (**11x**).* Yellow solid, mp = 73-75 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.68 (d, *J* = 16.1 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.28 (m, 3H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 8.3 Hz, 2H), 6.50 (d, *J* = 16.1 Hz, 1H), 4.20 (t, *J* = 6.6 Hz, 2H), 3.67 (s, 3H), 2.98 (t, *J* = 6.6 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.9, 151.7, 143.4, 136.4, 135.6, 129.7, 129.0, 128.7, 128.3, 127.1, 114.4, 109.6, 55.1, 46.1, 36.4; HRMS *m/z* [M+H^+] calcd for $C_{19}H_{20}N_3O$ 306.1601, found 306.1600.

*4.3.25 3-(2,3-Dichlorophenyl)-4-(naphthalen-1-ylmethyl)-4H-1,2,4-triazole (**11y**).* Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (s) and 8.08 (s) – total 1H, 7.93 (m) and 7.87 (m) – total 2H, 7.69 – 7.59 (m, 2H), 7.59 – 7.43 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.35 – 7.23 (m, 2H), 7.17 (d, *J* = 7.0 Hz) and 7.13 (d, *J* = 7.0 Hz) – total 1H, 5.66 (s) and 5.45 (s) – total 2H (biaryl restricted rotation conformers); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.6, 144.8, 143.9, 133.9, 133.8, 133.0, 132.6, 130.6, 130.5, 130.4, 130.2, 129.9, 129.8, 129.3, 129.2, 129.1, 129.0, 128.8, 127.8, 127.3, 127.2, 127.1, 126.6, 126.4, 125.6, 125.4, 125.2, 122.0, 121.9, 47.1, 47.0 (biaryl restricted rotation conformers); HRMS *m/z* [M+Na^+] calcd for $C_{19}H_{13}{}^{35}Cl_2N_3Na$ 376.0379, found 376.0381.

*4.3.26 4-tert-Butyl-3-(3,4-dimethylphenyl)-4H-1,2,4-triazole (**11z**).* Light orange solid, mp = 167-169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.22 – 7.09 (m, 3H), 2.30 (s, 3H), 2.27 (s, 3H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6, 138.5, 136.5, 131.6, 129.3, 128.0, 127.4, 57.27, 31.0, 19.6, 19.6; HRMS *m/z* [M+Na^+] calcd for $C_{14}H_{19}N_3Na$ 252.1471, found 252.1462.

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Supplementary data

The supplementary data containing NMR spectra of the reaction products is available on http://www.sciencedirect.com. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.10.018.

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23. Under the 1,2,4-triazole synthesis conditions, formamidrazones derived from aliphatic aldehydes (**12a-b**) decomposed while those derived from aromatic isocyanides (**12c-d**) remained largely unchanged. The latter observation appears to be consistent with the expected lower nucleophilicity of the aryl-substituted formamidrazone and its lower propensity to participate in the ring-forming process.