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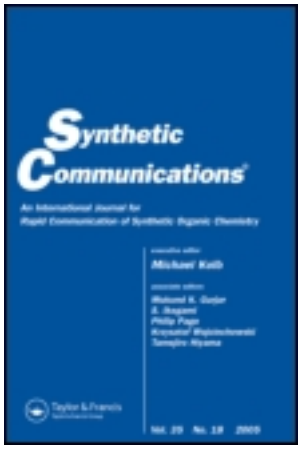

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Highly Regioselective Synthesis of 1,3,5-Trisubstituted 1,2,4-Triazole Derivatives

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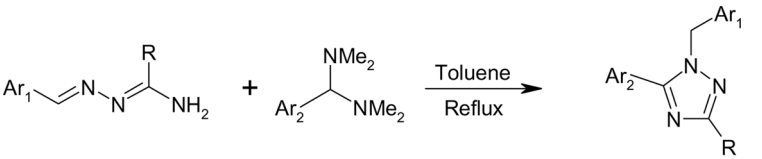
HIGHLY REGIOSELECTIVE SYNTHESIS OF 1,3,5-TRISUBSTITUTED 1,2,4-TRIAZOLE DERIVATIVES

David Ellis[1] and Aurelio Arias-Wood[2]
[1]*Discovery Chemistry, Pfizer Global Research and Development, Sandwich, Kent, UK*
[2]*Imperial College, London, UK*

GRAPHICAL ABSTRACT



Ar_1/Ar_2 = halophenyl, pyridyl, furyl
R = CH_3OCH_2-, t-BuO_2CNHCH_2-

Abstract *The synthesis of 1,3,5-trisubstituted-1,2,4-triazoles is described. The key reaction is* the thermal cyclization of an amidrazone intermediate with the aminal of an aromatic aldehyde*. The method allows a variety of functionalities to be incorporated to add diversity to the initial templates.*

Keywords Aminals; hydrazones; regioselective; thermal cyclization; 1,2,4-triazole

The 1,2,4-triazole template **A** (Fig. 1) was required as part of a medicinal chemistry program.

Several approaches to 1,3,5-trisubstituted 1,2,4-triazoles are known, but most lack a wider generality in synthesis. Some methods require the synthesis of specific hydrazines for use in a cyclization process, which may not be an attractive option when a variety of substituents is required.[1] Alkylation of 3,5-disubstituted 1,2,4-triazoles can lead to regioisomeric products that require separation by some means.[2] Other methods lack wider generality because of the use of intermediates that have lengthy syntheses[3] or require harsh reagents or conditions.[4]

A search of the literature revealed a 1,2,4-triazole by-product **B** in some work directed to the synthesis of triazaphospholes. This work utilized the cyclization of an amidrazone **1** with *tris*-dimethylaminophosphine[5] (Scheme 1). The authors suggested that breakdown of the amidrazone during the reaction gave rise to benzaldehyde, which reacted further with *tris*-dimethylaminophosphine to give the aminal.

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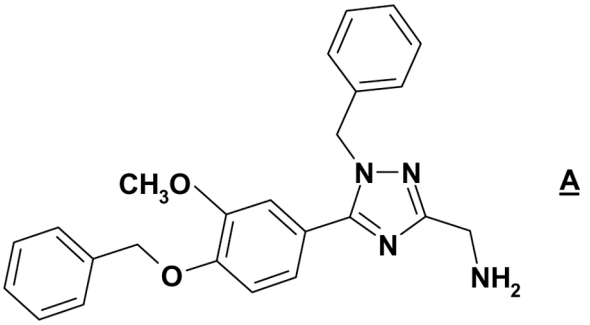

Figure 1. Initial triazole target.

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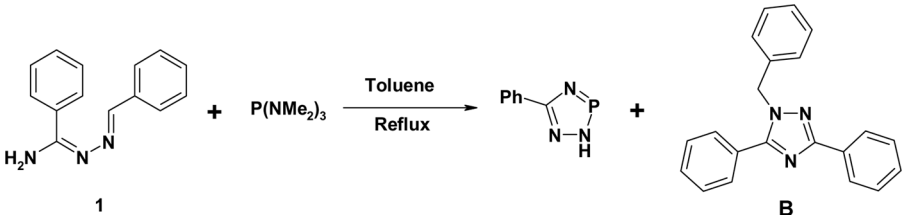
This then reacted with the amidrazone to produce the triazole **B** along with the triazaphosphole. This hypothesis was then proved in a separate experiment when amidrazone **1** was reacted with the tetramethylaminal of benzaldehyde in refluxing toluene to produce triazole **B** in 90% yield.

The conditions of the triazole-forming reaction are noteworthy for their simplicity, mildness, good yield, and regioselectivity. However, there are no reports of this reaction being used to make triazoles. This made us initially uncertain of the general applicability to the synthesis of the required triazoles. The reaction formed the basis of our own attempts to synthesize triazole **A** and later expand the process to include a variety of substituents.

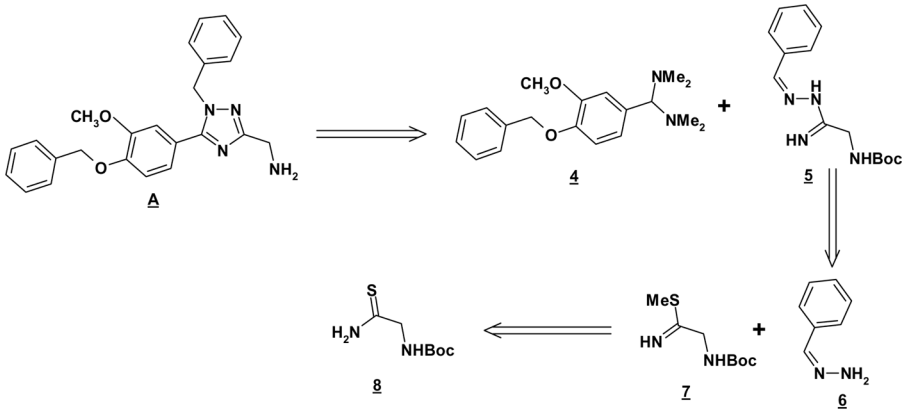
Retrosynthetic analysis of triazole **A** is shown in Scheme 2.

Aminal fragment **4** would be available from the corresponding commercially available aldehyde[6] while the amidrazone **5** can be conveniently derived from the hydrazone of benzaldehyde **6** and thioimidate **7**. The latter can be accessed by S-alkylation of the commercially available thioamide **8**.[7] The simple nature of the fragments in this synthesis suggested that other substituents could be easily introduced to produce a triazole synthesis of wider generality. The amidrazone fragment **5** already contains four of the atoms in the final triazole ring and is easily assembled in two steps under mild conditions[8] (Scheme 3).

Reaction of commercially available thioamide **8** with MeI in acetone at ambient temperature smoothly furnished the thioimidate salt, which was isolated by a simple filtration. Subsequent reaction with the hydrazone of benzaldehyde **6** in EtOH gave a clean reaction to yield the amidrazone **5**. A simple aqueous/organic



Scheme 1. Original literature synthesis with triazole by-product.



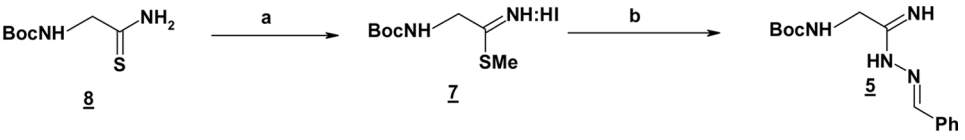
Scheme 2. Retrosynthetic analysis of the triazole **A**.

workup gave the free base of the amidrazone as a solid, which was pure enough for subsequent reactions.

N,N′-Dimethylaminal **4** was easily prepared by addition of a toluene solution of 4-benzyloxy-3-methoxybenzaldehyde to a solution of tris-dimethylaminoarsine in toluene.[9] A precipitate of As_2O_3 formed rapidly, and workup consisted of filtration and evaporation of the filtrate giving the aminal **4** as a clear oil, sufficiently pure for further reaction (Scheme 4).

To complete the synthesis of the triazole template **A**, the amidrazone **5** and aminal **4** were refluxed in toluene for 3 h. A simple aqueous/organic workup followed by column chromatography yielded the protected derivative of the desired triazole template **A** as a single regoisomer. The protecting group was removed by trifluoroacetic acid/dichloromethane (TFA/DCM) to furnish the required triazole **A** (Scheme 5).

Some early work in this area had established that neither aldehydes nor acetals were suitable to achieve this cyclization. Only the aminal gave a clean, rapid reaction. However, we were aware that utilization of arsenic-containing reagents for the synthesis of aminals would not endow the method with wide acceptance. We therefore sought an alternative method for the preparation of these intermediates. Aminals of aromatic aldehydes are frequently made by heating the aldehyde and 40% aqueous dimethylamine at 50–60 °C for several hours.[10] This protocol did not work well with 4-benzyloxy-3-methoxybenzaldehyde where very poor conversions were obtained. Further studies on aminal formation used p-bromobenzaldehyde.



a) MeI, acetone, RT,87% b) Benzaldehyde hydrazone, EtOH, RT,70%

Scheme 3. Synthesis of the amidrazone.

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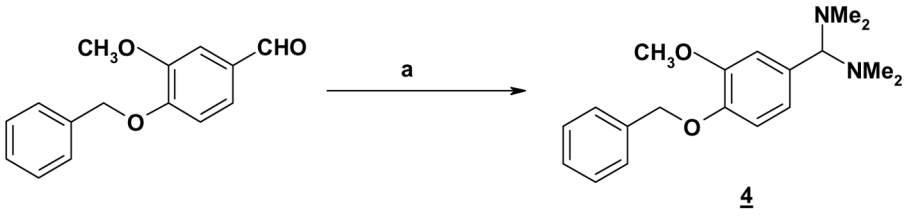

Scheme 4. Synthesis of the aminal.

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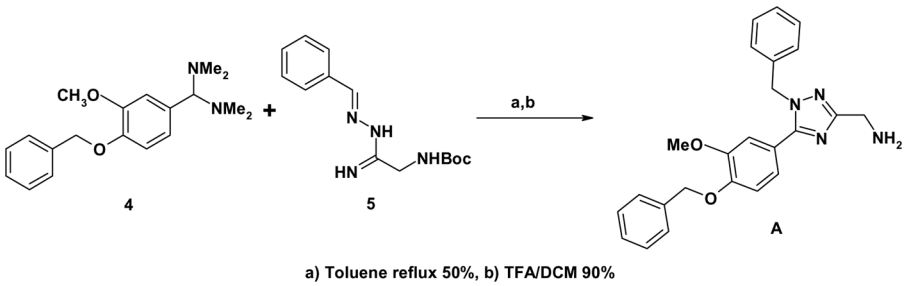
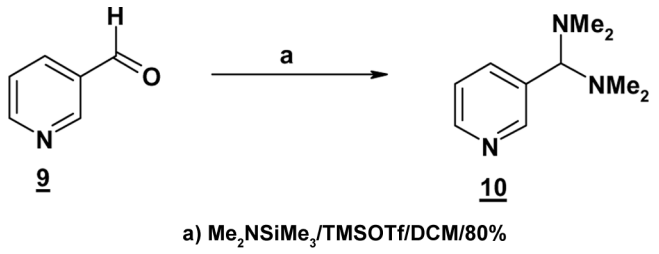
This aldehyde was chosen as it would be less electronically compromised and yet still yield triazole targets with useful functionality for further reactions. This aldehyde reacted well with 40% aqueous dimethylamine solution at 50 °C to produce the corresponding aminal. Simple evaporation of the solvent and azeotropic drying of the residue with toluene produced the aminal as a clear oil, which was sufficiently pure for subsequent use. Some residual aldehyde was seen by NMR. This could be easily estimated, and allowances were made in the subsequent step with the prior knowledge that it would not participate in the cyclization to the triazole.

A simpler and more rapid method was found later.[11] It is known that aromatic aldehydes can be transformed into their aminals with dimethylaminotrimethylsilane catalyzed by trimethylsilyltrifluoromethane sulfonate in DCM at 0 °C. This procedure was followed for pyridine-3-carboxaldehyde **9** and a good yield of the aminal **10** was obtained under these mild conditions (Scheme 6).



Scheme 5. Final cyclization to the triazole.



Scheme 6. Alternative synthesis of aminals.

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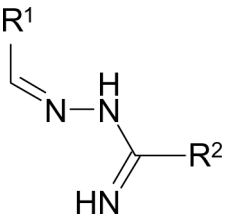
Once reliable methods had been established for aminal synthesis, attention turned to variation of the amidrazone fragment. The benzaldehyde originally used was readily replaced by other aromatic aldehydes such as p-bromobenzaldehyde, pyridine-3-carboxaldehyde, and furan-3-carboxaldehyde. The hydrazones were synthesized in the same manner from the aldehyde and hydrazine hydrate. The thioamide fragment was also varied to include methoxythioacetamide, which would furnish a useful masked alcohol substituent. After alkylation of these thioamides with MeI as before, the thioimidate salts reacted smoothly with the hydrazones to produce a range of amidrazones. A simple chromatographic purification was needed for the products (Table 1).

Reaction of the amidrazones with the aminals proceeded as before to give the expected 1,3,5-trisubstituted 1,2,4-triazoles in acceptable yields. A simple chromatography was required to give pure products, with the excess aminals always eluting first. The triazoles synthesized are shown in the table along with spectroscopic data (Table 2). All triazoles were produced as a single isomer. Extensive NMR profiling of

Table 1. NMR data for the amidrazones



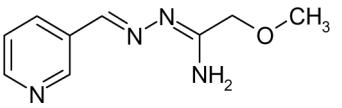
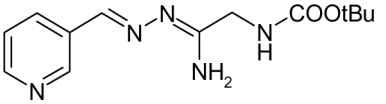
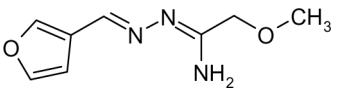
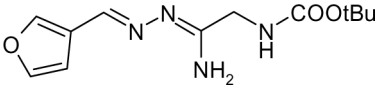
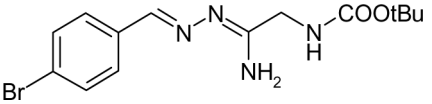
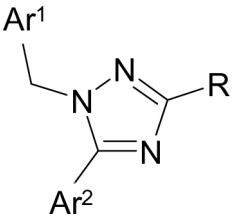
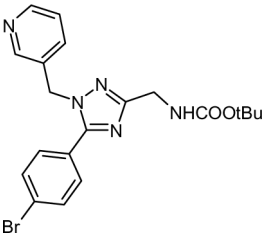
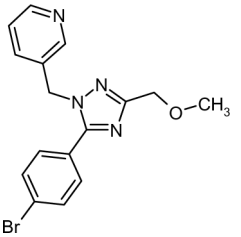
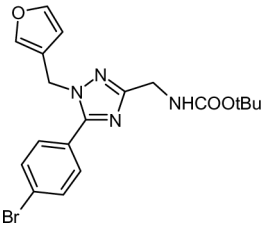
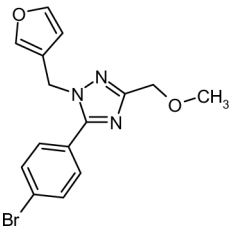
Amidrazone	NMR data
	δ ($CDCl_3$) 1.72–1.85 br s, 2H, 3.43 s, 3H, 4.15 s, 2H, 7.28–7.33 m, 1H, 8.03–8.08 m, 1H, 8.35 s, 1H, 8.60 m, 1H, 8.90 s, 1H. ESIMS: m/z 193 $[MH]^+$.
	δ ($CDCl_3$) 1.46 s, 9H, 3.95 m, 2H, 5.12–5.30 br m, 1H, 5.65–6.05 br m, 2H, 7.28–7.35 m, 1H, 8.05–8.10 m, 1H, 8.38 s, 1H, 8.58–8.63 m, 1H, 8.90 s, 1H. ESIMS: m/z 222 $[M - tBu]^+$.
	δ ($CDCl_3$) 1.50–1.70 br s, 2H, 3.42 s, 3H, 4.12 s, 2H, 6.80 s, 1H, 7.42 s, 1H, 7.70 s, 1H, 8.30 s, 1H. ESIMS: m/z 182 $[MH]^+$.
	δ ($CDCl_3$) 1.46 s, 9H, 3.88–3.95 m, 2H, 5.10–5.25 br m, 1H, 5.60–5.75 br m, 2H, 6.79 s, 1H, 7.42 s, 1H, 7.70 s, 1H, 8.30 s, 1H. ESIMS: m/z 211 $[M - tBu]^+$.
	δ ($DMSO\text{-}d_6$) 1.38 s, 9H, 3.67–3.75 m, 2H, 6.30–6.85 br m, 2H, 6.88–6.95 br m, 1H, 7.68 m, 2H, 7.77 m, 2H, 8.23 s, 1H. ESIMS: m/z 355/357 $[MH]^+$ 1 Br pattern.

Table 2. NMR data on final triazoles



Entry	Triazole	NMR data
1		δ ($CDCl_3$) 1.43 s, 9H, 4.40–4.53 m, 2H, 5.10–5.30 br m, 1H, 5.35 s, 2H, 7.27–7.30 m, 1H, 7.40 d ($J = 8.15$ Hz), 2H, 7.50–7.58 m, 1H, 7.62 d ($J = 8.15$ Hz), 2H, 8.45 s, 1H, 8.55–8.62 m, 1H. ESIMS: m/z 388/390 $[M - tBu]^+$ 1 Br pattern. 42% yield (amorphous solid).
2		δ ($CDCl_3$) 3.50 s, 3H, 4.60 s, 2H, 5.40 s, 2H, 7.25–7.35 m, 1H, 7.42 d ($J = 8.30$ Hz), 2H, 7.53–7.58 m, 1H, 7.62 d ($J = 8.30$ Hz), 2H, 8.46 s, 1H, 8.56–8.60 m, 1H. ESIMS: m/z 359/361 $[MH]^+$ 1 Br pattern. 33% yield (glass).
3		δ ($CDCl_3$) 1.42 s, 9H, 4.30–4.55 br m, 2H, 5.15–5.35 m, 3H (inc s for 3H @ 5.30), 7.00 d ($J = 8.10$ Hz), 1H, 7.35 s, 0.5H, 7.38–7.42 m, 1.5H, 7.45–7.50 m, 2H, 7.57–7.65 m, 2H. ESIMS: m/z 377/379 $[M - tBu]^+$ 1Br pattern. 33% yield (glass).
4		δ ($CDCl_3$) 3.50 s, 3H, 4.60 s, 2H, 5.20 s, 2H, 7.05 d ($J = 8.10$ Hz), 1H, 7.30–7.65 m, 6H. 59% yield (glass).

(*Continued*)

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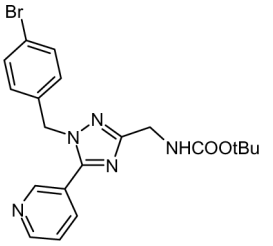
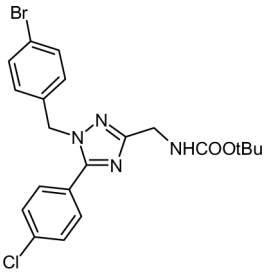
Table 2. Continued

Entry	Triazole	NMR data
5		δ ($CDCl_3$) 1.44 s, 9H, 4.40–4.55 m, 2H, 5.15–5.30 br m, 1H, 5.35 s, 2H, 7.05 d ($J = 8.10$ Hz), 2H, 7.38–7.44 m, 1H, 7.48 d ($J = 8.10$ Hz), 2H, 7.85–7.90 m, 1H, 8.70–8.75 m, 1H, 8.80 s, 1H. ESIMS: m/z 388/390 $[M - tBu]^+$ 1 Br pattern. 11% yield. (glass) (chromatographed twice).
6		δ ($CDCl_3$) 1.46 s, 9H, 4.40–4.53 m, 2H, 5.10–5.35 m, 3H (inc s for 2H @ 5.30), 7.05 d ($J = 8.16$ Hz), 2H, 7.38–7.50 m, 6H. ESIMS: m/z 421/423/425 $[M - tBu]^+$ 1Cl/1Br pattern. 65% yield (amorphous solid).

analog **2** confirmed the anticipated regiochemistry as shown. Carbon-13, heteronuclear multiple bond correlations (HMBC), and heteronuclear multiple quantum correlations (HMQC) NMR experiments were performed to establish the structure and hence the regioselectivity of the process.

CONCLUSION

A general approach to the synthesis of 1,3,5-trisubstituted 1,2,4-triazoles has been described. The desired regioselectivity has been confirmed by NMR studies. The method was successfully used in the preparation of a key target and related analogs containing substituents of value in medicinal chemistry. The method consists of several steps, but all are simple and mild. Initial studies utilizing an alternative aminal synthesis suggest that the method may have a broad applicability for such templates. The advantages over other methods include the avoidance of synthesizing particular hydrazines, the use of harsh reagents such as antimony pentachloride, cryogenic temperatures, and forcing thermal conditions.

EXPERIMENTAL

All ^1H NMR spectra were obtained on a 400-MHz Varian Mercury spectrometer using either $CDCl_3$ or dimethylsufoxide (DMSO-d_6) as solvents. The chemical shifts are reported in parts per million (ppm) relative to the deuterated solvent. Mass spectra were recorded on an Agilent 1100 series liquid chromatograph/mass spectrometer (LC/MS) in the electrospray/atmospheric pressure (ES/AP)

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ionization modes. All chromatography was performed using Merck silica gel using a gradient elution profile unless otherwise stated. Thin-layer chromatography (TLC) was performed using Merck TLC plates.

Representative Synthesis of the Hydrazones

To an ice-cold solution of hydrazine hydrate (0.94 g, 18.8 mmol) in EtOH (10 mL) was added a solution of benzaldehyde (2.00 g, 18.8 mmol) in EtOH (10 mL) dropwise under nitrogen over 10 min. The resulting solution was allowed to warm to ambient temperature. After 5 h, the solution was evaporated, and the residue was partitioned between EtOAc (30 mL) and water (15 mL). The organic phase was separated, washed with brine (15 mL), dried over $MgSO_4$, filtered, and evaporated to yield the product as a pale yellow oil, which solidified on storage in the freezer. Yield: 1.56 g, 66%; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.30$–5.65 (br s, 2H), 7.25–7.40 (m, 3H), 7.50–7.58 (m, 2H), 7.75 (s, 1H).

Data for the Hydrazones

Hydrazone of p-bromobenzaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.40$–5.70 (br s, 2H), 7.42 (d, 2H), 7.50 (d, 2H), 7.70 (s, 1H).

Hydrazone of furan-3-carboxaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.15$–5.60 (br s, 2H), 6.68 (s, 1H), 7.40 (s, 1H), 7.52 (s, 1H), 7.70 (s, 1H).

Hydrazone of pyridine-3-carboxaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.50$–5.85 (br s, 2H), 7.20–7.28 (m, 1H), 7.70 (s, 1H), 7.85–7.90 (m, 1H), 8.50 (br s, 1H), 8.66 (s, 1H).

Representative Synthesis of the Aminals

Trimethylsilyl-trifluoromethanesulfonate (61 mg, 50 μL, 0.28 mmol) was added dropwise as a solution in 3 mL DCM to an ice-cold solution of pyridine-3-carboxaldehyde (1 g, 9.34 mmol) and *N,N*-dimethylaminotrimethylsilane (2.3 g, 3.10 mL, 19.6 mmol) in DCM (7 mL), and the resulting solution was allowed to warm to ambient temperature. After 18 h the reaction mixture was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and evaporated to yield the product, which was sufficiently pure for further use. Yield: 1.56 g; 93% clear oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.07$ (s, 12H), 3.40 (s, 1H), 7.20–7.25 (m, 1H), 7.50 (d, 1H), 8.40 (s, 1H), 8.46 (d, 1H).

Aminal of P-Bromobenzaldehyde

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.10$ (s, 12H), 3.38 (s, 1H), 7.10 (d, 2H), 7.46 (d, 2H).

Representative Synthesis of the Thioimidates

Methyl iodide (556 mg, 3.92 mmol) was added in one portion to an ice-cold solution of N-t-butoxycarbonylaminothioacetamide (497 mg, 2.61 mmol) in acetone

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(5 mL). The resulting mixture was allowed to warm to ambient temperature. After 18 h, the mixture was filtered, and the precipitate was washed with ether and dried to furnish the product. Yield: 753 mg, 87%; amorphous white solid. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.38$ (s, 9H), 1.80–2.60 (br s, 2H), 2.70 (s, 2H), 4.35 (s, 2H), 6.35–6.42 (br s, 1H). There was evidence of rotamers in this spectrum, as is often seen with the Boc group.

Thioimidate of Methoxyacetic Acid Thioimidate

^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.80$ (s, 3H), 3.42 (s, 3H), 4.60 (s, 2H).

Representative Amidrazone Formation

A solution of benzaldehyde hydrazone (74 mg, 0.62 mmol) in EtOH (2 mL) dropwise was added to a stirred ice-cold solution of S-methyl-N-t-butoxycarbonyl-aminoacetylthioimidate and hydriodide salt (205 mg, 0.62 mmol) in EtOH (3 mL) over 2 min. The solution was allowed to warm to rt. After 18 h, the solvent was evaporated, and the residue was partitioned between EtOAc (10 mL) and 1 M NaOH (5 mL). The organic layer was separated, washed with brine (5 mL), dried over $MgSO_4$, filtered, and evaporated. The residue was triturated with ether and filtered to give the product as a white solid. Yield: 160 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.46$ (s, 9H), 3.95 (s, 2H), 5.15–5.30 (br s, 1H), 5.60–6.00 (br s, 2H), 7.35–7.40 (m, 3H), 7.70–7.75 (m, 2H), 8.38 (s, 1H). MS (APCI + ve): m/z (%) = 221 (100%) [$MH^+ - tBu$],

Representative Cyclization Procedure

A solution of the aminal (2 eq, 2 mmol) in toluene (2 mL) was added to a solution of an amidrazone (1 mmol, 1 eq) in toluene (8 mL). The resulting solution was heated to reflux under nitrogen for 3–5 h. The solution was then evaporated to dryness. The residue was purified by column chromatography using EtOAc/pentane or DCM/MeOH mixtures. Data on the final triazoles produced is included in Table 2.

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