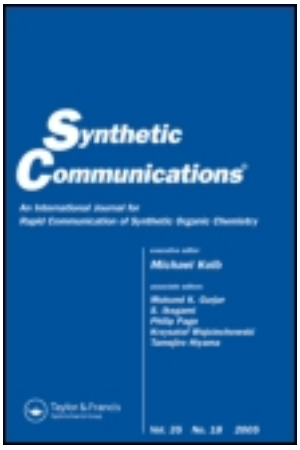

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Alternative Approach to 1,2,4-Triazole-3-carboxamides

David Ellis [a]
[a] Pfizer Global Research and Development , Sandwich, Kent, UK
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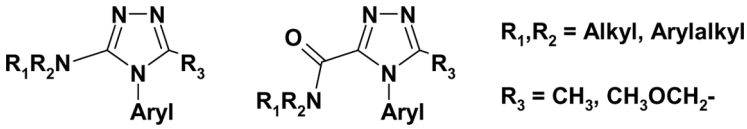
Alternative Approach to 1,2,4-Triazole-3-carboxamides

David Ellis
Pfizer Global Research and Development, Sandwich, Kent, UK

Abstract: The conversion of trichloromethyl and tribromomethyltriazoles to the corresponding carboxamide derivatives is described. The trihalomethyl analogs are straightforward to make and react readily with a range of amines to produce carboxamides. The strategy avoids the problems of decarboxylation associated with the use of triazole acids.

Keywords: 1,2,4-Triazole carboxamides, triazole carboxylic acids, trihalomethyloxadiazoles

We required a more convenient access to 3-amino- and 3-carboxamido-1,2,4-triazoles.[1]



Our established route, though robust, introduced the required amine variation in the first step. The rapid production of analogs was therefore hampered (Scheme 1).

In our hands, an alternative approach via the displacement of an activated leaving group such as chlorine had previously proved

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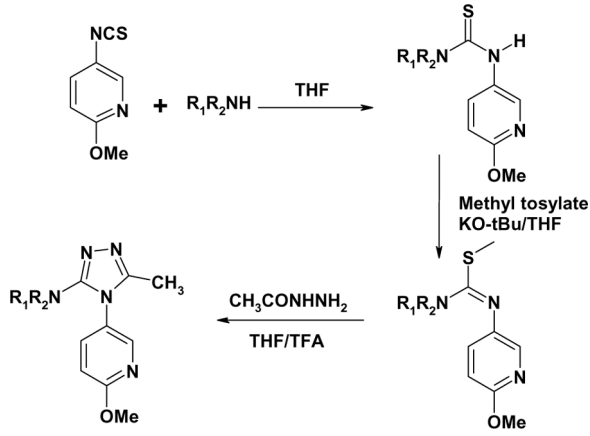
This paper is dedicated to the memory of Olga Wallace, a fine young chemist.

Address correspondence to David Ellis, Discovery Chemistry, Pfizer Global Research and Development, Ramsgate Road, Sandwich, Kent, CT13 9NJ, UK. E-mail: david.ellis@pfizer.com



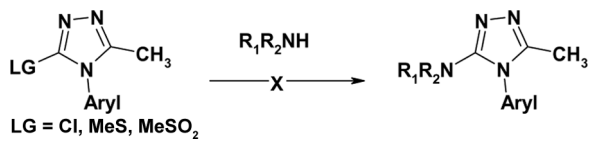
Scheme 1. Original synthesis of 5-amino-1,2,4-triazoles.

unsuccessful (Scheme 2), despite the frequent use of this strategy in heterocyclic chemistry.[2]

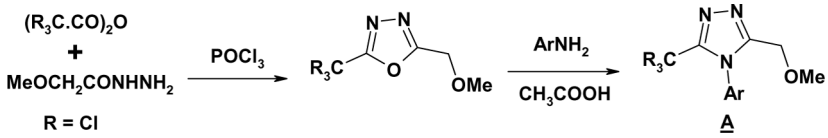
The literature indicated that the trichloromethyl group has some utility as a leaving group in this type of process with a variety of heterocycles,[3] though it has not been reported for 1,2,4-triazoles and its main use seems to be as a carboxylic acid surrogate.[4] This approach would require the requisite 3-trichloromethyl substituted 1,2,4-triazole **A**, which was synthesized by the well-established treatment of the corresponding 1,3,4-oxadiazole with an amine under acid catalysis[5] (Scheme 3).

The first attempt to convert A into an aminotriazole with piperidine was not successful, and the corresponding amide was produced instead (Scheme 4). This process appears unreported for 1,2,4-triazoles though occasionally is seen in six-membered heterocyclic systems[6] and also in a pyrazole template.[7] However, the conditions reported for the pyrazole template (refluxing ethanol) were unsuccessful for the triazole template.

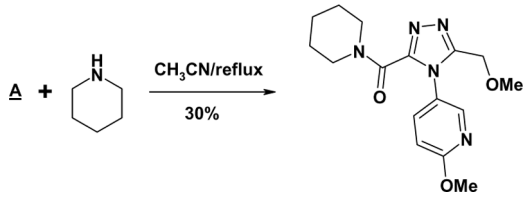
This appeared to be a general process, and after optimization, a small series of amides was synthesized rapidly using pyridine as a solvent and 4-dimethylaminopyridine as a catalyst (see Table 1). This alternative result was regarded as useful because previous attempts to access the



Scheme 2. Attempted displacement strategy.



Scheme 3. Synthesis of trichloromethyl-1,2,4-triazoles.

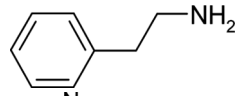
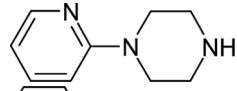
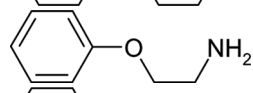
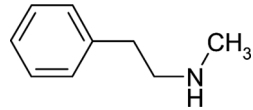
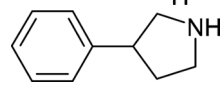
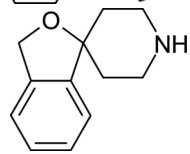


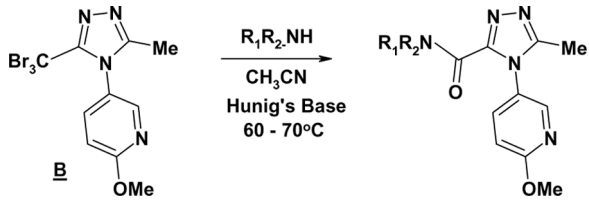
Scheme 4. Initial trial displacement reaction.

corresponding carboxylic acids had been thwarted by decarboxylation upon hydrolysis of the corresponding esters.[8]

The examples in the table show that the process tolerates some variety in the amine component.

Table 1. Reaction of trichloromethyltriazole A with various amines

Compound	Amine	Yield (%)
1		28
2		41
3		33
4		26
5		17
6		19

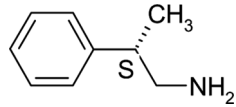
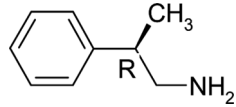
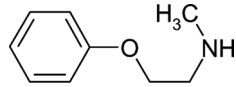


Scheme 5. Amidation reaction with tribromomethyltriazole.

The modest yields in the process may be due to chlorine being a poor leaving group, hence the greater temperatures and long reaction times. Bromine is a better leaving group, and the tribromomethyl group was tried in this conversion. Further literature work revealed[6] that the tribromomethyl group could be converted more easily to amides than the trichloromethyl analog in a six-membered heterocyclic system. Therefore, the tribromomethyl 1,2,4-triazole **B** was synthesized, and its conversion to amides was examined (Scheme 3, R = Br).

The conversion of triazole **B** to a small series of amides proceeded well under milder conditions than the trichloromethyl analog **A**. The reactions showed a much cleaner profile upon heating at 60–70°C in acetonitrile with Hunig's base. Yields of amide products also appeared to be more acceptable when compared to those obtained with the trichloromethyl analogs (Scheme 5, Table 2).

Table 2. Reaction of tribromomethyltriazole B with various amines

Compound	Amine	Yield (%)
7		48[a]
8		53[b]
9		72

[a]Ee of compound **7** is 95.4% (rt 12.9 min).

[b]Ee of compound **8** is 94% (rt 17.1 min). Determined on Chiralpak IA column with Heptane/IPA as eluent. This indicates that the chiral integrity has been maintained for these amines.

In summary, an alternative approach to 1,2,4-triazole-3-carboxamides has been found using the conversion of the tribromomethyl group with a variety of amines under mild conditions. This opens up further possibilities for this little used functional group interconversion.

EXPERIMENTAL

Proton nuclear magnetic resonance spectra (^{1}H NMR) data were obtained using a Varian 400-MHz Mercury spectrometer. Low-resolution mass spectral data were recorded on a Waters ZQ ESCI spectrometer. The quoted ions refer to the composition of the lowest isotopic mass. Column chromatography was performed using Merck silica gel 60 (230–400 mesh).

2-Methoxymethyl-5-trichloromethyl-1,3,4-oxadiazole

Preparation

Trichloroacetic anhydride (6.22 g, 20.14 mmol) was added dropwise over 5 min to methoxyacetic hydrazide (2.00 g, 19.21 mmol) with stirring under nitrogen at room temperature. (A mild exotherm was noted.) After stirring for 1 h, phosphorus oxychloride was added dropwise, and the resulting solution was heated to 110°C for 2 h. The reaction mixture was then cooled and evaporated to dryness. The residue was dissolved in ethyl acetate (30 ml), washed with saturated sodium bicarbonate solution (3×10 ml) and brine (10 ml), dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel using CH_2Cl_2/MeOH as eluent (100/0–97/3) to yield the product as a clear oil (1.72 g, 38%).

Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.5 (s, 3H), 4.75 (s, 2H). APCI + ve m/z 231/233/235 MH+ (three-chlorine pattern).

3-Methoxymethyl-4-(2-methoxy-5-pyridyl)-5-trichloromethyl-1,2,4-triazole

Preparation

5-Amino-2-methoxypyridine (1.07 g, 8.62 mmol) was added to a solution of 3-methoxymethyl-5-trichloromethyl-1,3,4-oxadiazole (1.33 g, 5.74

mmol) in glacial acetic acid (10 ml). The resulting solution was heated at 100°C for 2 h. The cooled reaction mixture was evaporated to dryness. The residue was dissolved in ethyl acetate (25 ml), washed with saturated sodium bicarbonate solution (2 × 10 ml), 10% aqueous citric acid solution (2 × 10 ml); and brine (10 ml); dried over $MgSO_4$; filtered; and evaporated. The residue was purified by chromatography on silica gel using ethyl acetate–pentane as eluent (0/100–100/0) to yield the product as a white solid (1.72 g, 54%).

Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (s, 3H), 4.07 (s, 3H), 4.53 (s, 2H), 6.85–6.95 (m, 1H), 7.25–7.35 (m, 1H), 7.84 (s, 1H). APCI + ve m/z 337/339/341 MH+ (three-chlorine pattern).

Conversion of Trichloromethyltriazole A into an Amide 1

Representative Procedure

2-Phenylethylamine (143 mg, 1.18 mmol) was added to a solution of the trichloromethyltriazole A (200 mg, 0.59 mmol) in pyridine (3 ml). 4-Dimethylaminopyridine (15 mg, 0.11 mmol) was added, and the resulting solution was heated to 100°C for 18 h under nitrogen. The cooled reaction mixture was evaporated and partitioned between ethyl acetate (10 ml) and water (5 ml). The organic phase was separated, washed with 1 M HCl (2 × 5 ml), saturated $NaHCO_3$ solution, and brine (5 ml); dried over $MgSO_4$; filtered; and evaporated. The residue was purified by chromatography on silica gel using CH_2Cl_2/MeOH as eluent (100/0–98/2) to furnish the product as a white solid (61 mg, 28%).

Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.87 (t, 2H), 3.30 (s, 3H), 3.62 (q, 2H), 4.00 (s, 3H), 4.42 (s, 2H), 6.85 (d, 1H), 7.17–7.32 (m, 5H), 7.40–7.55 (m, 1H), 7.55 (d, 2H), 8.10 (s, 1H). APCI + ve m/z 368 MH+. The following examples in this series were made by similar means.

Compound **2**. δ 3.35 (s, 3H), 3.65–3.85 (m, 6H), 4.00 (s, 3H), 4.10–4.25 (m, 2H), 4.45 (s, 2H), 6.65–6.80 (m, 2H), 6.85–6.90 (br d, 1H), 7.55–7.65 (m, 2H), 8.10 (s, 1H), 8.20–8.25 (br d, 1H). m/z 410 MH^+.

Compound **3**. δ 3.32 (s, 3H), 3.78 (q, 2H), 4.00 (s, 3H), 4.05–4.12 (m, 2H), 4.42 (s, 2H), 6.85–6.98 (m, 4H), 7.25–7.32 (m, 2H), 7.52–7.58 (br d, 1H), 7.75–7.87 (br t, 1H), 8.12 (s, 1H). m/z 384 MH^+.

Compound **4**. δ 2.85 & 3.05 (t, 2H), 3.22 & 3.32 (s, 3H), 3.66 & 4.10 (t, 2H), 3.95 & 4.00 (s, 3H), 4.40 & 4.45 (s, 2H), 6.77 & 6.83 (d, 1H), 7.10–7.35 (m, 6.5H), 7.60 (br d, 0.5H), 7.87 & 8.08 (s, 1H) (rotamers present in spectrum). m/z 382 MH^+.

Compound **5**. δ 2.00–2.20 (m, 1H), 2.30–2.50 (m, 1H), 3.30 & 3.33 (s, 3H), 3.38–3.65 (m, 2H), 3.80–4.12 (m, 2H), 4.00 (s, 3H), 4.32–4.40 (m, 0.5H), 4.42 & 4.45 (s, 2H), 4.55–4.62 (m, 0.5H), 6.85 (d, 1H), 7.20–7.38 (m, 5H), 7.57–7.63 (m, 1H), 8.06–8.10 (m, 1H). m/z 394 MH^+.

Compound **6**. δ 1.75–1.95 (m, 3H), 2.00–2.15 (m, 1H), 3.15–3.25 (m, 1H), 3.35 (s, 3H), 3.55–3.65 (m, 1H), 4.00 (s, 3H), 4.45 (s, 3H), 4.45–4.60 (m, 1H), 5.10 (s, 2H), 6.85 (d, 1H), 7.08–7.13 (m, 1H), 7.20–7.32 (m, 3H), 7.65 (dd, 1H), 8.13 (s, 1H). m/z 436 MH^+.

N-Acetyl-N′-tribromoacetylhydrazine

Preparation

A solution of tribromoacetyl chloride (4.46 g, 14.20 mmol) in 3 ml of acetonitrile was added to a stirred, ice-cold solution of acetic hydrazide (1.00 g, 13.50 mmol) and pyridine (1.28 g, 16.20 mmol) in acetonitrile (10 ml) dropwise over 5 min under nitrogen. The resulting dark solution was allowed to warm to room temperature. After 1 h the reaction mixture was evaporated to low volume and partitioned between dichloromethane and water. A precipitate formed, which was filtered, washed with small portions of dichloromethane and water, and dried under vacuum to yield the product as a white solid (2.00 g, 42%).

Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 9.50–9.90 (br s, 1H), 10.10–10.40 (br s, 1H). APCI−ve m/z 349–355 M−H+ for three-bromine pattern.

3-Methyl-5-tribromomethyl-1,3,4-oxadiazole

Preparation

Phosphorus oxychloride (1.4 g, 9.06 mmol, 845 μl) was added dropwise as a solution in acetonitrile (2 ml) to a refluxing solution of N-acetyl-N′-tribromoacetylhydrazine (1.60 g, 4.53 mmol) in acetonitrile (10 ml) under nitrogen. After 4 h, the reaction mixture was cooled to room temperature and evaporated to dryness. The residue was treated with ice to produce a white solid that was filtered, washed with water, and dried under vacuum to yield the product as a white solid (1.30 g, 85%).

Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H). APCI + ve m/z 350–356 MNH_4^+ for three-bromine pattern. Anal. calcd. for $C_4H_3Br_3N_2O$: C, 14.34; H, 0.90; N, 8.36. Found: C, 14.20; H, 0.89; N, 8.23.

3-Methyl-4-(2-methoxy-5-pyridyl)-5-tribromomethyl-1,2,4-triazole

Preparation

5-Amino-2-methoxypyridine (343 mg, 2.76 mmol) was added to a solution of 3-methyl-5-tribromomethyl-1,3,4-oxadiazole (617 mg, 1.84 mmol) in glacial acetic acid (5 ml). The resulting solution was heated at 60°C for 4 h and then left at room temperature overnight. The reaction mixture was evaporated to dryness, and the residue was azeotroped with toluene (2 × 5 ml). The residue was partitioned between dichloromethane (30 ml) and water (10 ml). The organic phase was separated washed with saturated sodium bicarbonate solution (10 ml), 10% aqueous citric acid solution (2 × 10 ml), and brine (10 ml); dried over $MgSO_4$; filtered; and evaporated. The residue was dissolved in refluxing methanol (20 ml) and decolorized with charcoal. After filtration and evaporation, a white solid was produced. This was triturated in ether, filtered, washed with fresh ether, and dried under vacuum to yield the product as a white solid (350 mg, 44%).

Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 4.00 (s, 3H), 6.90–6.95 (d, 1H), 7.65–7.70 (d, 1H), 8.30 (s, 1H). APCI + ve m/z 439/441/443/445 MH+ (three-bromine pattern).

Conversion of Tribromomethyltriazole B into Amide 7

Representative Procedure

Di-isopropylethylamine (103 mg, 0.80 mmol) was added to a solution of the tribromomethyltriazole B (101 mg, 0.23 mmol) and S-2-methyl-2-phenylethylamine (62 mg, 0.45 mmol) in acetonitrile (3 ml). The resulting solution was refluxed for 6 h under nitrogen. The cooled reaction mixture was evaporated and partitioned between ethyl acetate (10 ml) and water (5 ml). The organic phase was separated, washed with 1 M HCl (2 × 5 ml), saturated $NaHCO_3$ solution, and brine (5 ml); dried over $MgSO_4$, filtered, and evaporated. The residue was purified by chromatography on silica gel using EtOAc/pentane as eluent (20/80–100/0) to furnish the product as a white solid (39 mg, 48%).

Data

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (d, 3H), 2.35 (s, 3H), 2.95–3.05 (m, 1H), 3.35–3.50 (m, 1H), 3.55–3.65 (m, 1H), 4.00 (s, 3H), 6.88 (d, 1H), 7.15–7.35 (m, 6H), 7.40–7.45 (br d, 1H), 8.10 (s, 1H) m/z 352 MH^+. The other examples in this series were made by similar means.

Compound **8**. δ 1.27 (d, 3H), 2.35 (s, 3H), 2.95–3.05 (m, 1H), 3.35–3.50 (m, 1H), 3.55–3.65 (m, 1H), 4.00 (s, 3H), 6.88 (d, 1H), 7.15–7.35 (m, 6H), 7.40–7.45 (br d, 1H), 8.10 (s, 1H) m/z 352 MH^+.

Compound **9**. δ 2.36 (s, 3H), 3.13 & 3.55 (s, 3H), 3.82 (t, 1H), 3.93 & 3.98 (s, 3H), 4.10 (t, 1H), 4.27 (s, 2H), 6.75–6.88 (m, 3H), 6.92–7.00 (m, 1H), 7.25–7.32 (m, 2H), 7.47–7.55 (m, 1H), 8.02–8.08 (m, 1H) m/z 368 MH^+.

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