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1,3,4-Oxadiazole and Heteroaromatic-Fused 1,2,4-Triazole Synthesis using Diverted Umpolung Amide Synthesis

Kazuyuki Tokumaru, Kalisankar Bera, and Jeffrey N. Johnston

Department of Chemistry, and Institute of Chemical Biology, Vanderbilt University, Nashville, TN 37235

Abstract

Umpolung Amide Synthesis (UmAS) has emerged as a superior alternative to conventional amide synthesis methods based on carbonyl electrophiles in a range of situations, particularly when epimerization-prone couplings are prescribed. In an unanticipated development during our most recent studies, it was discovered that diacyl hydrazide products from UmAS were not formed as intermediates when using an acyl hydrazide as the amine acceptor. This resulted in a new preparation of 1,3,4-oxadiazoles from α -bromonitroalkane donors. We hypothesized that a key tetrahedral intermediate in UmAS was diverted toward a more direct pathway to the heterocycle product rather than through formation of the diacyl hydrazide, a typical oxadiazole progenitor. In studies reported here, diversion to 1,2,4-triazole products is described, a behavior hypothesized to also result from an analogous tetrahedral intermediate, but one formed from heteroaromatic hydrazine acceptors.

Graphical abstract

Keywords

oxadiazole; triazole; diverted Umpolung Amide Synthesis; triazolopyridine; pyrazine; pyrimidine; pyridazine; hydrazine

Introduction

Aromatic heterocycle synthesis is a mainstay of medicinal chemistry, organometallic chemistry, and natural product synthesis. A tremendous number of heterocycle preparations are based upon the dehydration – either actual or formal – of precursors to the heterocycle,

involving carbon-heteroatom bond formation and elimination.¹ Another large group of approaches involve oxidative transformations of an aromatic heterocycle's precursor.² Syntheses of both 1,3,4-oxadiazoles^{3,4,5} and 1,2,4-triazoles largely fall into these two categories.⁶ Collectively, these approaches often invoke the use of highly electrophilic reagents or strong oxidants, and some have noted the inefficient nature (i.e. a large mass of reagent-derived waste) typical of these reactions.¹ These approaches have enabled the discovery and development of small molecules effective against an array of protein targets, including the oxadiazoles zibotentan,⁷ raltegravir,⁸ and setileuton,⁹ or the triazoles GS-458967¹⁰ and **1**¹¹ (Figure 1). Others have yielded improved materials.¹²

Heterocycles bearing side chains with a chiral center at the point of attachment to the aromatic ring can be particularly challenging, yet highly important targets. In a recent example, the triazolopyridine AMG 337 (**2**) was discovered as an inhibitor of the enzyme c-Met tyrosine kinase, an intervention point for various forms of cancer (Figure 1).¹³ Its synthesis was accomplished through dehydrative cyclization of an acyl hydrazide intermediate. The preparation of enantiopure material relied on the availability of (*S*)-(-)-methyl lactate.

We recently reported a novel pathway to construct a 1,3,4-oxadiazole ring from α -bromo nitroalkane and acyl hydrazide under newly optimized conditions for UmAS.^{14,15,16} Control experiments indicated that the mechanistic diversion point between amide and oxadiazole formation may be after the formation of the hypothesized tetrahedral intermediate (Scheme 1, **3a**). We also became interested in the synthesis of triazole heterocycles from heteroaryl hydrazines as an outgrowth of oxadiazole synthesis, based on the hypothesis that they might share a possible mechanistic intersection point in **3b** (Scheme 1) and the analogous cyclization. If successful, the approach might extend to a broad range of fused heterocyclic species, owing to the commercial availability and synthetic accessibility of heteroaryl hydrazines. We report here experimental support for this analogy, thereby extending our earlier findings that α -bromonitronate chemistry can be redirected to azole products, instead of the acylated product that would normally result. Furthermore, broad classes of aromatic fused triazoles can be prepared through this approach. The yields are moderate to good using a KI/UHP protocol, the activating reagents are inexpensive, and the reaction produces co-products that are easily removed by a straightforward aqueous wash.

Results and Discussion

The synthesis of oxadiazoles was recently reported by modification of an UmAS approach (Table 1).¹⁴ Aside from their attractive features for drug development,¹⁷ innovative new uses for oxadiazoles continue to emerge, as do methods for their synthesis.¹⁸ A complement of experiments in the oxadiazole synthesis revealed that the expected diacyl hydrazide was not an intermediate. However, this was unanticipated, yet consistent with the formation of a tetrahedral intermediate hypothesized in our prior work (Scheme 1).¹⁹ This tetrahedral intermediate was diverted from the diacyl hydrazide, directly to the heterocyclic product by intramolecular cyclization. Rather generous changes to both the α -bromo nitroalkane donor and the acyl hydrazide acceptor were tolerated, as judged by yields ranging from 43% to 81%. This procedure was optimized using UHP as the stoichiometric oxidant, and potassium

iodide (KI) as the initiator for halonium formation. This protocol combines the benefit of an inexpensive iodine source and stoichiometric peroxide oxidant. In this reaction, controlling the generation rate for the iodonium species by slow addition of UHP is crucial to achieve good yields, presumably to limit acyl hydrazide overoxidation, a process that would draw the electrophilic acyl diazene intermediate away from productive reaction with an α -bromo nitroalkane.^{14,15}

A similar intermediate **3b** (Scheme 1) might be formed by substitution of the acyl hydrazide acceptor with a 2-pyridyl hydrazine. From the intermediate, the pyridine ring might provide a nitrogen heteroatom as an alternative to oxygen for further cyclization. In contrast to the oxadiazole produced from an acyl hydrazide, this aryl hydrazine should result in a fused triazole product.

Optimized conditions for the KI/UHP-mediated nitronate coupling were applied to **8a**, resulting in 57% yield of the desired triazolopyridine (**9a**) (Table 2, Series A). Attempts to further optimize this reaction, using conditions parallel to those applied to acyl hydrazides, did not improve upon this protocol. The trifluoromethyl-substituted 2-pyridyl hydrazine **8b** delivered triazolopyridine **9b** in 57% yield. Finally, a 6-chloro-substituted case (**8c**) established further generality in this series, while also providing a substitutionally-labile heterocyclic backbone substituent in **9c**.

The pyrazine product series was targeted next (Table 2, Series B). The parent pyrazine (**8d**) provided the triazole product (**9d**) in 57% yield, suggestive of some generality in the overall approach. Exhibiting a similar trend to series A above, the 3-chloro-substituted case (**8e**) provided the annulated triazole product **9e** in 48% yield.

The analogy by which successful extensions to bicyclic fused heterocycles were made was further tested by the question whether the more electron-rich 2-hydrazino thiazole could be an effective substrate (Table 2, Series C). In the event, a 4-phenylthiazole-derived hydrazine (**8f**) provided thiazolotriazole **9f** in 52% yield. An additional example involved the benzothiazole-fused tricycle **9g** that formed in a slightly lower yield (42%).

Attempts to further hop across heterocyclic scaffolds led to triazoles fused to benzoxazole (**9h**), pyrimidine (**9i**), and pyridazine (**9j**) in 30%, 48%, and 48% yields, respectively (Table 2, Series D). Each of these further extends the value of the α -bromonitroalkane approach to 5-substituted fused triazoles. The aim of these studies was to establish the generality of the approach rather than an optimization for any one heterocycle class.

The value of this approach was further highlighted by the use of chiral nonracemic α -bromo nitroalkane donors^{20,21} to prepare triazole derivatives (Table 3). The first case was met with minimal success, as pyridyltriazole **12** was formed in approximately 24% yield. It was not clear whether the depressed yield was to be attributed to the donor, so the analogous pyrazine was used. Not only was the yield (61%) of **13** substantially improved relative to this first case, it was superior to the first cases examined in this series (Table 2, Series B). This encouraged additional attempts that included **14–16**, in 42%, 76%, and 76% yield, respectively. The conservation of configuration in each case is unsurprising based on the

mechanism of these reactions; the key umpolung carbon-nitrogen bond formation before the carbon atom is converted from sp^3 to sp^2 in the triazole avoids the formation of an epimerizable intermediate. This is a significant advantage of this approach, in contrast to alternatives based on condensative hydrazide and heterocycle synthesis, where epimerization is consistently noted.^{4,13}

The behavior of α -bromo nitroalkane donors with acyl hydrazides and heteroaryl hydrazines extends the utility of the UmAS approach to oxadiazole and triazole heterocycles, including the broad classes of fused triazoles outlined here. The mechanistic picture on which these studies launched hypothesized the tetrahedral intermediate common to UmAS. Its collapse to a diacyl hydrazide, however, was expected but not observed. We reason that the fate of the tetrahedral intermediate instead diverted to oxadiazole and triazole heterocycles after nitro-nitrite isomerization.^{22,23} At the nitrite stage, a polar mechanism can then be leveraged by intramolecular cyclization, and after an elimination step, heterocycle formation is complete. The basic KI/UHP protocol is optimal here for its ability to maintain a steady, low concentration of halonium, a feature that not only leads to serviceable yields, but also visibly enhances selective product formation as evidenced by NMR analysis of crude reaction mixtures. Although mechanistically distinct, the combination of iodide, oxidant, and base is reminiscent of the conditions (I_2 , K_3PO_4 , DMSO, 100 °C) developed by Wu to prepare oxadiazoles from methyl ketone and acyl hydrazide.²⁴

In conclusion, a unique triazole synthesis has been developed based on α -bromo nitroalkane feedstock and the notion that hydrazine acceptors could lead to acylated hydrazines. A mechanism-based diversion from tetrahedral intermediates **3a–b** is reasoned to explain the findings that oxadiazole and triazole products are formed without intermediacy of an acylated hydrazine. As a result, the dehydrative conditions necessary for conversions of hydrazides to these heterocycles are replaced by mild oxidative conditions that effect the key carbon-nitrogen bond forming step. Coupled to this protocol is the ability to merge advances in enantioselective α -bromo nitroalkane synthesis, resulting in enantiopure heterocycles (i.e. **12–16**).

Experimental Section

All reagents and solvents were commercial grade and purified prior to use when necessary. Flash column chromatography was performed using Sorbent Technologies 40–63 mm, pore size 60 Å silica gel with solvent systems indicated. Analytical thin layer column chromatography was performed using Sorbent Technologies 250 mm glass-backed UV254 silica gel plates, and were visualized by fluorescence upon 250 nm radiation and/or the by use of ceric ammonium molybdate, ninhydrin, or potassium permanganate. Solvent removal was effected by rotary evaporation under vacuum (~ 25–40 mm Hg). All extracts were dried with sodium sulfate unless otherwise noted.

Nuclear magnetic resonance spectra (NMR) were acquired on a Bruker AV-400 (400 MHz), Bruker DRX-500 (500 MHz), or Bruker AV II-600 (600 MHz) instrument. Chemical shifts are measured relative to residual solvent peaks as an internal standard ($CHCl_3$ at 7.26 ppm in 1H NMR, 77.16 ppm in ^{13}C NMR), unless otherwise specified. Mass spectra were recorded

on a Thermo Electron Corporation MAT 95XP-Trap mass spectrometer by use of the ionization method noted by the Indiana University Mass Spectrometry Facility. IR spectra were recorded on a Nicolet Avatar 360 spectrophotometer and are reported in wavenumbers (cm^{-1}) as neat films on a NaCl plate (transmission). Melting points were obtained using an OptiMelt automated melting point system (Stanford Research Systems). Optical rotations were measured on a Perkin Elmer-341 polarimeter.

General Procedure for the Synthesis of Fused Triazoles

To a vigorously stirred mixture of α -bromo nitroalkane (0.50 mmol), heteroaryl hydrazine (0.60 mmol, 1.2 equiv), potassium iodide (1.0 mmol, 2.0 equiv) and potassium carbonate (1.0 mmol, 2.0 equiv) in 1,2-dimethoxyethane (5.0 mL) was added a solution of urea-hydrogen peroxide in 4:1 1,2-dimethoxyethane-water (0.50 M solution, 1.0 mL, 0.50 mmol, 1.0 equiv) over 2 h by syringe pump at room temperature. After the addition was complete, the mixture was stirred for an additional 4 h. Aqueous sodium thiosulfate was then added and the mixture was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography to give pure fused triazole.

3-(4-Chlorobenzyl)-[1,2,4]triazolo[4,3-a]pyridine (9a)

Yield: 28 mg (from 0.20 mmol of **7**, 57%); colorless solid; mp 170-173 °C; R_f = 0.30 (10% methanol/ethyl acetate).

IR (film): 3043, 1494, 1428, 1391, 1344, 1092, 778 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.76 (d, J = 9.4 Hz, 1H), 7.29-7.27 (m, 2H), 7.68 (d, J = 6.8 Hz, 1H), 7.22 (dd, J = 9.4, 6.8 Hz, 1H), 7.18-7.16 (m, 2H), 6.75 (t, J = 6.8 Hz, 1H), 4.52 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3): ppm 150.3, 144.8, 133.4, 133.1, 129.7, 129.2, 126.9, 122.0, 116.7, 113.9, 30.7.

HRMS (ESI): Exact mass calcd for $\text{C}_{13}\text{H}_{11}\text{ClN}_3$ $[\text{M}+\text{H}]^+$ 244.0642, found 244.0640.

3-(4-Chlorobenzyl)-6-(trifluoromethyl)-[1,2,4]triazolo[4,3-a]pyridine (9b)

Yield: 71 mg (from 0.40 mmol of **7**, 57%); colorless solid; mp 141-144 °C; R_f = 0.32 (ethyl acetate).

IR (film): 3028, 1489, 1324, 1173, 1133, 1092, 1036, 811 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 8.06 (d, J = 1.3 Hz, 1H), 7.88 (d, J = 9.6 Hz, 1H), 7.36 (dd, J = 9.6, 1.3 Hz, 1H), 7.34-7.31 (m, 2H), 7.22-7.19 (m, 2H), 4.55 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3): ppm 149.7, 146.3, 133.8, 132.3, 129.8, 129.4, 122.9 (q, J = 2.1 Hz), 122.7 (q, J = 271.7 Hz), 121.5 (q, J = 5.9 Hz), 118.5 (q, J = 34.6 Hz), 117.9, 30.5.

HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{10}\text{ClF}_3\text{N}_3$ $[\text{M}+\text{H}]^+$ 312.0515, found 312.0506.

5-Chloro-3-(4-chlorobenzyl)-[1,2,4]triazolo[4,3-a]pyridine (9c)

Yield: 77 mg (from 0.5 mmol of **7**, 55%); colorless solid; mp 163-165 °C; R_f = 0.17 (ethyl acetate).

IR (film) 3042, 1629, 1495, 1411, 1310, 1202, 1074, 992, 791 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 7.70 (dd, J = 9.2, 0.8 Hz, 1H), 7.25 (d, J = 8.5 Hz, 2H), 7.14 (dd, J = 9.2, 7.0 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 6.77 (dd, J = 7.0, 0.8 Hz, 1H), 4.83 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3) ppm 152.3, 146.2, 135.7, 132.8, 129.7, 128.9, 127.6, 125.2, 115.6, 114.9, 33.2.

HRMS (ESI): Exact mass calcd for $\text{C}_{13}\text{H}_{10}\text{Cl}_2\text{N}_3$ $[\text{M}+\text{H}]^+$ 278.0252, found 278.0265.

3-(4-Chlorobenzyl)-[1,2,4]triazolo[4,3-a]pyrazine (9d)

Yield: 28 mg (from 0.20 mmol of **7**, 57%); colorless solid; mp 166-169 °C; R_f = 0.32 (10% methanol/ethyl acetate).

IR (film): 3102, 2985, 1491, 1094, 1013, 781 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 9.35 (d, J = 1.6 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.60 (dd, J = 4.8, 1.6 Hz, 1H), 7.33-7.31 (m, 2H), 7.19-7.17 (m, 2H), 4.56 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3): ppm 145.9, 145.8, 144.9, 133.9, 132.2, 129.9, 129.8, 129.5, 114.8, 30.6.

HRMS (ESI): Exact mass calcd for $\text{C}_{12}\text{H}_{10}\text{ClN}_4$ $[\text{M}+\text{H}]^+$ 245.0594, found 245.0603.

8-Chloro-3-(4-chlorobenzyl)-[1,2,4]triazolo[4,3-a]pyrazine (9e)

Yield: 54 mg (from 0.40 mmol of **7**, 48%); colorless solid; mp 154-157 °C; R_f = 0.43 (ethyl acetate).

IR (film): 3095, 1611, 1474, 1384, 1281, 1091, 955, 774 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): δ 7.59 (d, J = 4.7 Hz, 1H), 7.56 (d, J = 4.7 Hz, 1H), 7.33-7.30 (m, 2H), 7.18-7.15 (m, 2H), 4.56 (s, 2H).

^{13}C NMR (100 MHz, CDCl_3): ppm 147.8, 144.1 (2C), 133.9, 131.9, 129.8, 129.5, 128.7, 114.8, 30.8.

HRMS (ESI): Exact mass calcd for $\text{C}_{20}\text{H}_{25}\text{N}_4\text{O}_2$ $[\text{M}+\text{H}]^+$ 353.1978, found 353.1974.

3-(4-Chlorobenzyl)-5-phenylthiazolo[2,3-c][1,2,4]triazole (9f)

Yield: 34 mg (from 0.20 mmol of **7**, 52%); colorless solid; mp 224-227 °C; R_f = 0.30 (ethyl acetate).

IR (film): 3032, 1469, 1174, 1090, 1017, 816, 766, 701 cm^{-1} .

¹H NMR (400 MHz, CDCl₃): δ 7.59 (d, *J* = 4.7 Hz, 1H), 7.56 (d, *J* = 4.7 Hz, 1H), 7.33-7.30 (m, 2H), 7.18-7.15 (m, 2H), 4.56 (s, 2H).

¹³C NMR (100 MHz, CDCl₃): ppm 158.4, 146.6, 133.9, 132.6, 130.9, 130.4, 129.6, 129.4, 128.9, 128.5, 128.3, 114.2, 31.4.

HRMS (ESI): Exact mass calcd for C₁₇H₁₃ClN₃S [M+H]⁺ 326.0519, found 326.0517.

3-(4-Chlorobenzyl)benzo[4,5]thiazolo[2,3-*c*][1,2,4]triazole (9g)

Yield: 62 mg (from 0.5 mmol of **7**, 41% yield); colorless solid; mp 163-165 °C; *R*_f = 0.31 (ethyl acetate).

IR (film) 3061, 2926, 1489, 1429, 1324, 1262, 1090, 1013, 820, 749 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.69-7.64 (m, 1H), 7.43-7.39 (m, 1H), 7.38-7.33 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 4.60 (s, 2H).

¹³C NMR (100 MHz, CDCl₃) ppm 156.4, 147.6, 133.5, 133.2, 132.6, 129.7, 129.6, 129.4, 126.8, 126.3, 124.9, 114.0, 32.0.

HRMS (ESI): Exact mass calcd for C₁₅H₁₁ClSN₃ [M+H]⁺ 300.0362, found 300.0355.

7-Chloro-3-(4-chlorobenzyl)benzo[4,5]oxazolo[2,3-*c*][1,2,4]triazole (9h)

Yield: <47 mg (from 0.5 mmol of **7**, <30% yield); colorless solid; mp 165-167 °C; *R*_f = 0.30 (ethyl acetate).

IR (film) 3073, 2923, 1568, 1468, 1254, 1080, 815, 731 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, *J* = 2.0 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 7.21 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.44 (s, 2H).

¹³C NMR (100 MHz, CDCl₃) ppm 163.5, 153.5, 144.4, 134.0, 132.9, 132.1, 129.9, 129.6, 125.2, 123.1, 114.1, 113.1, 32.3.

HRMS (ESI): Exact mass calcd for C₁₅H₁₀Cl₂N₃O [M+H]⁺ 318.0201, found 318.0214.

3-(4-Chlorobenzyl)-[1,2,4]triazolo[4,3-*a*]pyrimidine (9i)

Yield: 58 mg (from 0.5 mmol of **7**, 48%); colorless solid; mp 190-192 °C; *R*_f = 0.17 (ethyl acetate:methanol = 9:1).

IR (film) 3099, 2932, 1506, 1401, 1279, 1096, 935, 771 cm⁻¹.

¹H NMR (400 MHz, CD₃OD) δ 8.73 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.65 (dd, *J* = 7.2, 2.0 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 2H), 7.30 (d, *J* = 8.8 Hz, 2H), 7.08 (dd, *J* = 7.2, 4.0 Hz, 1H), 4.56 (s, 2H).

¹³C NMR (100 MHz, CD₃OD) ppm 157.2, 155.3, 146.9, 134.8, 134.6, 133.4, 131.5, 130.3, 111.7, 30.9.

HRMS (ESI): Exact mass calcd for C₁₂H₁₀ClN₄ [M+H]⁺ 245.0594, found 245.0588.

6-Chloro-3-(4-chlorobenzyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (9j)

Yield: 67 mg (from 0.5 mmol of **7**, 48%); colorless solid; mp 178-180 °C; R_f = 0.24 (ethyl acetate).

IR (film) 3069, 1479, 1414, 1325, 1152, 1079, 1011, 954, 771 cm⁻¹.

¹H NMR (400 MHz, CDCl₃) δ 8.05 (d, *J* = 9.6 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 9.6 Hz, 1H), 4.51 (s, 2H).

¹³C NMR (100 MHz, CDCl₃) ppm 149.5, 148.9, 143.0, 133.4, 133.3, 130.6, 129.0, 126.5, 122.3, 29.8.

HRMS (ESI): Exact mass calcd for C₁₂H₉Cl₂N₄ [M+H]⁺ 279.0204, found 279.0208.

***tert*-Butyl (*R*)-(1-([1,2,4]triazolo[4,3-*a*]pyridin-3-yl)-3-phenylpropyl)carbamate (12)**

Yield: <42 mg (from 0.50 mmol of **10**, <24%); colorless solid; mp 164-167 °C; R_f = 0.27 (ethyl acetate).

$$[\alpha]_D^{20} + 27.4 (c 1.0, \text{CHCl}_3)$$

IR (film): 3321, 2978, 1694, 1511, 1366, 1251, 1167, 1037, 913, 863, 743 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 8.18 (d, *J* = 6.8 Hz, 1H), 7.77 (ddd, *J* = 9.2, 1.1, 1.1 Hz, 1H), 7.29-7.25 (m, 3H), 7.21-7.17 (m, 3H), 6.82 (ddd, *J* = 6.8, 6.8, 1.1 Hz, 1H), 5.26-5.20 (m, 1H), 5.02 (d, *J* = 9.6 Hz, 1H), 2.85-2.80 (m, 2H), 2.65 (dddd, *J* = 14.4, 7.6, 7.6, 7.6 Hz, 1H), 2.50 (dddd, *J* = 14.4, 7.9, 7.9, 7.9 Hz, 1H), 1.44 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): ppm 155.7, 150.3, 147.3, 140.7, 128.6 (2C), 127.3, 126.3, 123.2, 116.4, 113.8, 80.5, 44.8, 35.0, 32.1, 28.4.

HRMS (ESI): Exact mass calcd for C₂₀H₂₅N₄O₂ [M+H]⁺ 353.1978, found 353.1974.

***tert*-Butyl (*R*)-(1-([1,2,4]triazolo[4,3-*a*]pyrazin-3-yl)-3-phenylpropyl)carbamate (13)**

Yield: 107 mg (from 0.50 mmol of **10**, 61%); colorless solid; mp 99-102 °C; R_f = 0.43 (ethyl acetate).

$$[\alpha]_D^{20} + 15.1 (c 1.0, \text{CHCl}_3)$$

IR (film): 3258, 2977, 1697, 1512, 1366, 1252, 1167, 1045, 916, 864, 735 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ 9.33 (d, *J* = 1.2 Hz, 1H), 8.16-8.15 (br m, 1H), 7.85 (d, *J* = 4.8 Hz, 1H), 7.29-7.26 (m, 2H), 7.22-7.14 (m, 3H), 5.24-5.18 (m, 1H), 5.04 (d, *J* = 9.2 Hz, 1H), 2.87-2.76 (m, 2H), 2.67 (dddd, *J* = 14.3, 7.3, 7.3, 7.3 Hz, 1H), 2.54 (dddd, *J* = 14.3, 7.7, 7.7, 7.7 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): ppm 155.7, 148.3, 145.6, 144.3, 140.2, 129.7, 128.6, 128.5, 126.3, 116.1, 80.7, 44.6, 34.5, 32.0, 28.3.

HRMS (ESI): Exact mass calcd for $\text{C}_{19}\text{H}_{23}\text{N}_5\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 376.1749, found 376.1749.

***tert*-Butyl (*R*)-([1,2,4]triazolo[4,3-*a*]pyrazin-3-yl(4-chlorophenyl)methyl)carbamate (14)**

Yield: 75 mg (from 0.5 mmol of **10**, 42%); viscous colorless oil; R_f = 0.35 (ethyl acetate).

$$[\alpha]_D^{20} - 12.1 (c\ 1.0, \text{CHCl}_3).$$

IR (film) 3289, 2978, 1700, 1503, 1367, 1265, 1167, 1031, 739 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 9.34 (d, J = 1.5 Hz, 1H), 7.87 (d, J = 4.7 Hz, 1H), 7.82 (dd, J = 4.7, 1.5 Hz, 1H), 7.35 (s, 4H), 6.35 (d, J = 8.0 Hz, 1H), 6.03 (d, J = 8.0 Hz, 1H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) ppm 155.2, 147.0, 145.9, 144.7, 135.4, 135.0, 130.2, 129.5, 129.1, 115.3, 81.1, 49.8, 28.4.

HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{18}\text{ClN}_5\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 382.1047, found 382.1046.

***tert*-Butyl (*R*)-([1,2,4]triazolo[4,3-*a*]pyrazin-3-yl(4-chlorophenyl)methyl)carbamate (15)**

Yield: 150 mg (from 0.5 mmol of **10**, 76%); viscous colorless oil; R_f = 0.35 (ethyl acetate).

$$[\alpha]_D^{20} - 16.1 (c\ 1.0, \text{CHCl}_3).$$

IR (film) 3295, 2981, 1699, 1506, 1363, 1265, 1168, 1039, 905, 733 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 9.35 (s, 1H), 7.91 (d, J = 4.5 Hz, 1H), 7.86 (d, J = 4.5 Hz, 1H), 7.56 (brs, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.38 (d, J = 7.8 Hz, 1H), 6.23 (brs, 1H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) ppm 155.2, 146.9, 145.9, 144.8, 139.1, 132.2, 130.8, 130.7, 130.2, 126.3, 123.3, 115.3, 81.2, 49.8, 28.4.

HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{19}\text{BrN}_5\text{O}_2$ $[\text{M}+\text{H}]^+$ 404.0722, found 404.0720.

***tert*-Butyl (*R*)-([1,2,4]triazolo[4,3-*a*]pyrazin-3-yl(4-chlorophenyl)methyl)carbamate (16)**

Yield: 130 mg (from 0.5 mmol of **10**, 76%); viscous colorless oil; R_f = 0.35 (ethyl acetate).

$$[\alpha]_D^{20} - 27.5 (c\ 1.0, \text{CHCl}_3).$$

IR (film) 3283, 2970, 1701, 1505, 1362, 1270, 1171, 1036, 905, 747 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 9.33 (d, J = 1.5 Hz, 1H), 7.81 (d, J = 4.8 Hz, 1H), 7.78 (dd, J = 4.8, 1.5 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.32 (d, J = 8.0 Hz, 1H), 6.06 (d, J = 8.0 Hz, 1H), 2.33 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3) ppm 155.2, 147.5, 145.9, 144.7, 139.0, 133.8, 130.1, 129.9, 127.6, 115.3, 80.8, 50.5, 28.4, 21.3.

HRMS (ESI): Exact mass calcd for $\text{C}_{18}\text{H}_{22}\text{N}_5\text{O}_2$ $[\text{M}+\text{H}]^+$ 340.1774, found 340.1769.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
1,3,4-Oxadiazoles and Heteroaromatic-Fused 1,2,4-Triazoles in Therapeutic Development

Scheme 1.

Intersection of Oxadiazole and Triazole Synthesis Using Diverted UmAS

Table 1

Preparation of 1,3,4-Oxadiazoles Using an UmAS Protocol

Table 2

Reaction Scope for the Diverted UmAS Synthesis of Fused Triazoles

Table 3Application of Diverted UmAS to the Synthesis of Fused Bicyclic Triazoles Bearing an α -Chiral Center