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Copper-promoted synthesis of 1,4-benzodiazepinones via alkene diamination

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Abstract

A new method for the synthesis of 2-aminomethyl functionalized 1,4-benzodiazepin-5-ones is presented. The benzodiazepine core is well-known to interact with biological receptors and many pharmaceutical drugs are derived from this structure. The alkene diamination strategy is employed for the first time for the synthesis of 1,4-benzodiazepinones. In this reaction, copper(2-ethylhexanoate)₂ serves as promoter and a range of external amines can be coupled with 2-sulfonamido-*N*-allyl benzamides to generate the 1,4-benzodiazepinones in good yields.

Keywords

1, 4-benzodiazepinones; diamination; copper-promoted; alkenes

Benzodiazepines and related compounds are considered privileged structures in medicinal chemistry.^{1–3} A sampling of 1,4-benzodiazepines and 1,4-benzodiazepinones and their corresponding biological activities are illustrated in Figure 1.^{4–7} While methods involving coupling of anthranilic acid (2-aminobenzoic acid) derivatives and either amino acids or amines and aldehydes (Ugi reaction) are most frequently used for 1,4-benzodiazepinone synthesis,^{8,9} an emerging strategy involves coupling of anthranilic acid derivatives with allylic amines followed by transition-metal facilitated ring closure via alkene difunctionalization (Scheme 1). These methods have enabled the synthesis of variously functionalized 1,4-benzodiazepines and 1,4-benzodiazepinones not readily synthesized by the more classical routes.

Palladium-catalyzed alkene oxidative amination,¹⁰ carboamination^{11–13} and aminoacetoxylation¹⁴ have all been performed to secure the 1,4-benzodiazepinone core while introducing various benzyl, alkenyl and acetoxymethyl functional groups on the

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benzodiazepine ring (Scheme 1). Despite these advances, no method for benzodiazepine formation via alkene diamination has yet been reported. Aminomethyl-functionalized benzodiazepines have demonstrated interesting biological activity (Fig. 1), thus a versatile method for their synthesis would be a valuable contribution. We report herein a copper-promoted intra/intermolecular alkene diamination for the synthesis of aminomethyl-functionalized 1,4-benzodiazepinones (Scheme 1).

Over the past decade, alkene diamination has emerged as a powerful way to access valuable 1,2-diamines.^{15–24} Such vicinal diamines have demonstrated significant utility as components of bioactive compounds, as well as in chemical synthesis, where they are useful as either ligands or catalysts in organic and organometallic transformations.^{15,25,26} Our research group has developed copper-promoted^{27–29} and copper-catalyzed²³ alkene diaminations for the synthesis of aminomethyl functionalized indolines, isoindolines, pyrrolidines, γ -lactams, cyclic ureas, cyclic sulfamides, tetrahydroisoquinolines and tetrahydroquinolines. While transition metal catalyzed cyclization reactions to form larger rings are generally more challenging than five-membered ring formation reactions, the successful precedent set by the palladium-catalyzed alkene difunctionalizations (Scheme 1) convinced us that formation of 1,4-benzodiazepinones via copper-facilitated alkene diamination should be feasible. The reduction in transannular strain due to the high prevalence of sp^2 -hybridized carbons in the diazepinone backbone may favor cyclization compared to formation of seven-membered rings made up of predominantly Csp^3 -backbone.

The reaction of *N*-nosyl-2-amino-*N'*-allylbenzamide **1a** in the presence of $TsNH_2$ (3 equiv), $Cu(2\text{-ethylhexanoate})_2$ and Cs_2CO_3 (1 equiv) was examined under various conditions for the formation of 1,4-benzodiazepinone **2a** (Table 1). Using 300 mol% $Cu(2\text{-ethylhexanoate})_2$ in either xylenes at 130 °C or $PhCF_3$ at 120 °C for 48 h, 100% conversion of substrate **1a** was observed and 1,4-benzodiazepinone **2a** was isolated in 81% and 76% yields, respectively (Table 1, entries 1 and 2). A decrease in either reaction time or $Cu(2\text{-ethylhexanoate})_2$ loading led to decreased conversion (Table 1, entries 3 and 4). 1,2-Dichloroethane at 105 °C were also viable reaction conditions and provided 80% conversion to **2a** after 48 h (Table 1, entry 5). When catalytic $Cu(2\text{-ethylhexanoate})_2$ (30 mol%) in the presence of MnO_2 (300 mol %) was used, less than 5% conversion to diamine **2a** was observed (Table 1, entry 6).

The scope of the diamination reaction was next explored using the reaction conditions in Table 1, entry 1 unless otherwise noted (Scheme 2). As illustrated in Scheme 2, various 2-sulfonamido-*N*-allyl benzamide derivatives **1** underwent copper-promoted cyclization and coupling with various external amine sources such as tosamide, benzamide, 2-trimethylsilylethylsulfonamide ($SESNH_2$), cyclopropylsulfonamide, 4-trifluoromethylaniline and various arylsulfonamides. Isolated yields of 2-aminomethyl functionalized 1,4-benzodiazepin-5-ones **2** ranged from 40–79%. Lower loading (2 equiv) of both benzamide and 4-trifluoromethylaniline to provide **2e** and **2k** respectively resulted in higher conversion, possibly due to higher levels of coordination of these amines to the copper(2-ethylhexanoate)₂, which might result in reduced reactivity. Interestingly, the nosyl-functionalized substrate that generates **2a** (Table 1, entry 1) was more reactive than the tosyl-functionalized substrate that generates **2b** (Scheme 2). This is the reverse of the reactivity pattern previously observed in related copper(2-ethylhexanoate)₂ promoted alkene

aminoxxygenation reactions that provide 5-membered pyrrolidine products.³⁰ This may indicate that the formation of a less reversible or more stable N-[Cu] complex³¹ of **1** could involve deprotonation of the sulfonamide (more facile with *N*-nosyl than *N*-tosyl) which could be more kinetically significant in the more challenging seven-membered ring formation.

An amide whose cyclization/diamination would have resulted in a regioisomeric 1,4-benzodiazepine-5-one did not react (Figure 2). A substrate bearing a 1,1-disubstituted alkene and a substrate lacking an amide alkyl group (in other words, free amide NH) also did not react (Figure 2). Finally, a substrate bearing an internal, styrenyl alkene, did not react (Figure 2). The lack of reactivity with the styrenyl alkene supports a more concerted alkene addition mechanism rather than one based on *N*-radical formation and addition to the alkene as the *N*-radical would be expected to be more reactive with the styrenyl alkene than with a terminal alkene.

A potential mechanism for the diamination reaction is illustrated in Scheme 3. Following coordination of [Cu(II)] to the sulfonamide of substrate **1a**, cis-aminocupration³¹ through a nine-membered ring transition state provides the unstable organocopper(II) intermediate **4**. Homolysis of the C-[Cu(II)] bond results in organic radical **5** and [Cu(I)]. Addition of radical **5** to [Cu(II)] and concomitant coordination of TsNH₂ provides an organocopper(III) intermediate **6**.³² Carbon-nitrogen bond formation via reductive elimination then generates the 1,4-benzodiazepin-5-one product **2a**.

In summary, the synthesis of 2-aminomethyl functionalized 1,4-benzodiazepin-5-ones **2** has been enabled by copper-promoted alkene diamination. Investigation into the bioactivity of these interesting new compounds is underway and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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33. Representative diamination procedure (Table 1, entry 1): *4-methyl-N-((1-((4-nitrophenyl)sulfonyl)-5-oxo-4-phenyl-2,3,4,5-tetrahydro-1H-benzo[e][1,4]diazepin-2-yl)methyl)benzenesulfonamide (2a)*: *N*-allyl-2-((4-nitrophenyl)sulfonamido)-*N*-phenylbenzamide (**1a**) (50 mg, 0.11 mmol, 1 equiv) in a glass tube equipped with a magnetic stir bar was treated with Cs₂CO₃ (37.1 mg, 0.11 mmol, 1 equiv), *p*-toluenesulfonamide (58.6 mg, 0.34 mmol, 3 equiv) and copper(2-ethylhexanoate)₂ (120 mg, 0.34 mmol, 3 equiv) followed by 0.6 mL (0.2 M) of xylenes. The tube was capped and the reaction mixture was stirred at 130 °C for 48 h. The reaction mixture was allowed to cool to room temperature and then was diluted with CH₂Cl₂ (10 mL). This mixture was then washed with sat. aq. EDTANa₂ (2 x 10 mL) and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (3 x 25 mL). The organic layers were combined, dried with Na₂SO₄ and concentrated *in vacuo* to yield the crude product, which was purified by flash chromatography on silica gel (20–80% EtOAc in hexanes gradient) to afford the benzodiazepinone **2a** in 81% yield (56 mg, 0.09 mmol) as a white solid. mp: 118–130 °C; ¹H NMR (400 MHz, CDCl₃) δ 2.48 (s, 3H), 3.02–2.97 (m, 1H), 3.15–3.12 (m, 1H), 3.44 (dd, *J* = 15.6, 12.4 Hz, 1H), 3.86 (dd, *J* = 15.6, 4.8 Hz, 1H), 4.72–4.67 (m, 1H), 5.20 (t, *J* = 6.0 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 2H), 7.20–7.17 (m, 2H), 7.28–7.24 (m, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.57–7.51 (m, 2H), 7.74–7.70 (m, 3H), 7.78 (d, *J* = 8.0 Hz, 2H), 8.09 (d, *J* = 8.8 Hz, 2H) ppm; ¹³C

NMR (75 MHz, CDCl₃) δ 21.6, 44.5, 51.8, 62.2, 123.9, 124.5, 126.8, 127.3, 128.8, 129.0, 130.0, 130.2, 130.8, 130.9, 132.4, 132.5, 135.4, 136.0, 141.0, 143.6, 144.1, 150.3, 166.9 ppm; IR (neat, thin film) ν 3266, 2925, 2360, 1644, 1596, 1531, 1494, 1455, 1402, 1349, 1164, 1091 cm⁻¹; HRMS (ESI) calcd. for C₂₉H₂₇O₇N₄S₂ [M+H]⁺ 607.1316, found 607.1318

Figure 1.
Examples of biologically active 1,4-benzodiazepinones

Figure 2.
Unreactive substrates

Previous work: Pd-catalyzed carboamination and aminoacetoxylation **This work: copper-promoted diamination**

Scheme 1.

Scheme 2.

Scope of the benzodiazepinone-forming alkene diamination

Scheme 3.
Proposed diamination mechanism

Table 1

Optimization of the diamination^a

Entry	Cu(II) (mol %)	Solvent	Temp (°C)	T (h)	Yield (%)
1	300	xylenes	130	48	81 ^b
2	300	PhCF ₃	120	48	76 ^b
3	300	PhCF ₃	120	24	90% conversion
4	200	PhCF ₃	120	48	64% conversion
5	300	DCE	105	48	80% conversion
6	30	xylenes	130	48	<5% conversion

^aReactions were run in capped glass tubes heated in oil baths.^bIsolated yield following chromatography on silica gel. No substrate was present in crude ¹H NMR (100% conversion).