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# Synthesis of Chiral 3-Substituted 1,3,4,5-Tetrahydro-1,4-benzodiazepin-2-ones *via* a Domino Copper-Catalyzed $S_N2$/Coupling Reaction

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**Abstract:** A novel protocol for the facile synthesis of chiral 3-substituted 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-ones *via* a domino reaction has been developed, which involves a cascade of $S_N2$ nucleophilic substitution and copper-catalyzed C–N coupling reactions of α-amino acid amides and *ortho*-halobenzyl halides. This protocol has some merits, such as one-pot process, easy operation, a wide scope of substrates. Furthermore, no heavy racemization occurs during the reaction.

**Keywords:** α-amino acid amides; cross-coupling; domino reactions; nucleophilic substitution; 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-ones

Compounds with [1,4]benzodiazepine skeletons comprise valuable pharmaceuticals against anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and so on.[1] To date, thousands of different benzodiazepines have been synthesized and about thirty of them are in clinical use in various parts of the world.[1]

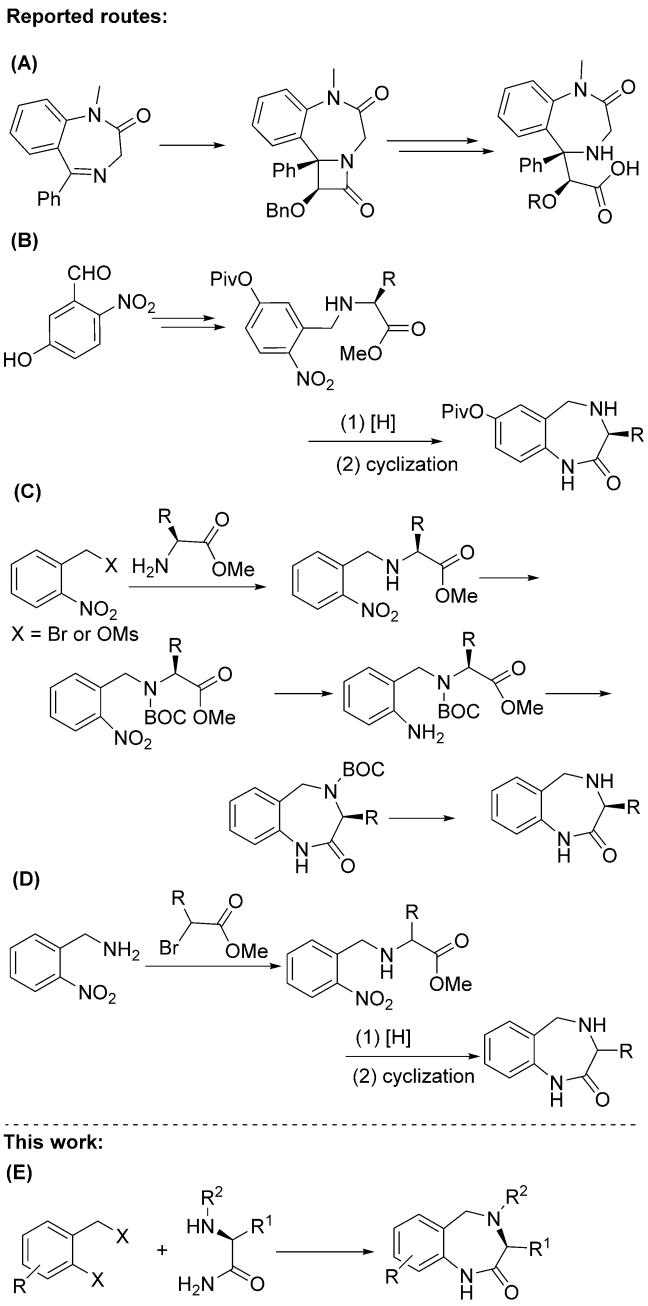
Most common benzodiazepine drugs are characterized by a 3*H*-1,4-benzodiazepin-2-one skeletal unit, such as diazepam, bromazepam, camazepam, cinolazepam, clonazepam, and clorazepate. These compounds have been proven invaluable in contemporary neuropsychiatry. However, compounds with a 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one scaffold have demonstrated promising diverse pharmacological activities in recent researches, such as endothelin receptor antagonists,[2] anti-HIV agents,[3] anti-ischemic agents,[4] peptidomimetics for G-protein coupled receptors (GPCRs),[5] membrane-type receptor for bile acids (M-BAR or TGR5) receptor agonists,[6] and modulators of retinoic acid receptor (RAR)-related orphan receptor-gamma.[7] Therefore it is imperative to explore novel and facile synthetic methods for diverse 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-ones based on a variety of available substrates.

Four synthetic routes of 1,3,4,5-tetrahydrobenzo[*e*]-[1,4]diazepin-2-one derivatives have been reported upto now (Scheme 1, routes **A** to **D**). These routes consist of (i) diastereoselective [2+2] cycloaddition of 3,5-dimethoxyphenoxyketene and 1,3-dihydrobenzo[*e*][1,4]diazepin-2-ones (Scheme 1, route **A**);[2] (ii) condensation, reductive alkylation, catalytic hydrogenation and subsequent intramolecular cyclization with 2-nitrobenzaldehyde and amino acid esters as starting materials (Scheme 1, route **B**);[5,7] (iii) $S_N2$ substitution of *ortho*-nitrobenzyl bromide or methanesulfonate and amino acid esters with or without BOC-protection and reduction and cyclization (Scheme 1, route **C**);[3,4,8] (iv) nucleophilic substitution, hydrogenation, condensation with *ortho*-nitrobenzylamines and α-bromoacetate as starting materials (Scheme 1, route **D**).[3] Thus, the reported methods commonly need two to five transformations for the synthesis of 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-ones. This leaves room for research into synthetic methodologies of higher efficiency, which is a salient goal of organic synthesis.[9]

In this context, domino reactions, in which multiple reactions are combined into one synthetic operation are ideal since they do not involve work-up and isolation of numerous intermediates.[10] Copper-catalyzed coupling is a feasible approach for heterocycle synthesis.[11] As part of our ongoing research on coupling[12] and domino reactions,[13] a domino copper-catalyzed $S_N2$/C–N coupling reaction of α-amino acid amides and *ortho*-halobenzyl halides is described herein, as shown in Scheme 1, route **E**.

The model substrates initially used to evaluate the domino reaction were 2-iodobenzyl bromide and L-phenylalaninamide (Table 1). It was observed that

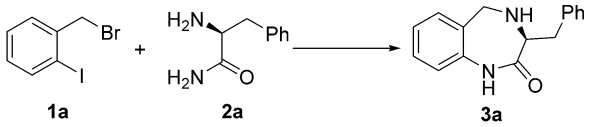



**Scheme 1.** The reported (**A** to **D**) and our new (**E**) synthetic routes of 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-ones.

CuCl, CuBr and CuI could all promote this reaction (entries 1-3), with the latter being the best catalyst (entry 3). $Cu_2O$ and CuO also promoted the reaction (entries 4 and 5), but to a lesser degree than CuI.

For the aforementioned domino reaction, the polarity of the solvent is an important parameter. Low polarity solvents such as toluene gave nearly no product (entry 6). As a general observation, higher yields were obtained with increasing polarity of the solvent (entries 3, 6–8) with DMF being the best one (entry 3). Stronger bases did not afford higher yields

**Table 1.** Optimization of the conditions for the domino Cu-catalyzed $S_N2$/coupling reaction.[a]




| Entry | Catalyst | Solvent | Base | Yield [%][b] |
|---|---|---|---|---|
| 1 | CuCl | DMF | $K_2CO_3$ | 46 |
| 2 | CuBr | DMF | $K_2CO_3$ | 54 |
| 3 | CuI | DMF | $K_2CO_3$ | 92 |
| 4 | $Cu_2O$ | DMF | $K_2CO_3$ | 79 |
| 5 | CuO | DMF | $K_2CO_3$ | 76 |
| 6 | CuI | toluene | $K_2CO_3$ | trace |
| 7 | CuI | dioxane | $K_2CO_3$ | 44 |
| 8 | CuI | DMA | $K_2CO_3$ | 87 |
| 9 | CuI | DMF | $Cs_2CO_3$ | 90 |
| 10 | CuI | DMF | *t*-BuONa | 41 |
| 11[c] | CuI | DMF | $K_2CO_3$ | 82 |
| 12 | CuI | DMF | $K_2CO_3$ | 47 (42)[d] |
| 13 | – | DMF | $K_2CO_3$ | 0 (84)[e] |

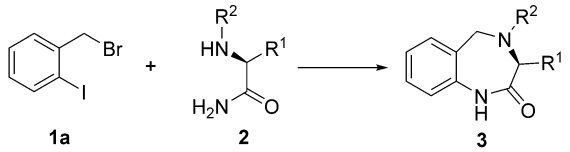
[a] *Reaction conditions:* 2-iodobenzyl bromide (0.5 mmol), L-phenylalaninamide (0.75 mmol), CuI (0.05 mmol), $K_2CO_3$ (1 mmol), DMF (5 mL), 110 °C, 24 h, unless otherwise stated.
[b] Isolated yield.
[c] 90 °C.
[d] 12 h; (*S*)-2-(2-iodobenzylamino)-3-phenylpropanamide (**4**) (44% yield).
[e] No CuI, 1 h; (*S*)-2-(2-iodobenzylamino)-3-phenylpropanamide (**4**) (84% yield).

(entries 9 and 10). Furthermore, a decrease of the temperature or shortening of the reaction time was not conducive to this reaction (entries 11 and 12).

It was noted that besides the target product, (*S*)-2-(2-iodobenzylamino)-3-phenylpropanamide (**4**), the product of $S_N2$ nucleophilic substitution was also isolated from the reaction mixture when only half of the reaction time was used (Entry 12). It is the only product when the reaction was performed without CuI for only one hour (entry 13). This information signifies that the domino reaction under examination includes a $K_2CO_3$-promoted $S_N2$ nucleophilic substitution at first and then a CuI-catalyzed intramolecular C–N coupling reaction.

With the optimized conditions at hand, various amino acid amides were examined to react with 2-iodobenzyl bromide (Table 2). Most L-form amino acid amides are commercially available, but the DL- and D-forms are not. As such, DL-phenylalaninamide was synthesized according to the literature,[14] and it gave nearly the same yield as the L-form (entries 2 *vs.* 1). Chiral HPLC analysis demonstrated that the *ee* value of the product of L-phenylalaninamide was 96% ee, which means that about 2% to 3% of L-phenylalaninamide was racemized during the domino reaction.

**Table 2.** Examination of various amino acid amides to react with 2-iodobenzyl bromide.[a]




1a 2 3

| Entry | $R^1$ | $R^2$ | Amino acid amide | Product | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | Bn | H | L-phenylalaninamide | L-**3a** | 92[c] |
| 2 | Bn | H | DL-phenylalaninamide | DL-**3a** | 93 |
| 3 | Me | H | L-alaninamide | L-**3b** | 78[d] |
| 4 | Me | H | D-alaninamide | D-**3b** | 75[e] |
| 5 | Me | H | DL-alaninamide | DL-**3b** | 80 |
| 6 | Et | H | L-butyrinamide | **3c** | 56 |
| 7 | *i*-Pr | H | L-valinamide | **3d** | 85 |
| 8 | *i*-Bu | H | L-leucinamide | **3e** | 91 |
| 9 | Ph | H | L-phenylglycinamide | **3f** | 58 |
| 10 | $-(CH_2)_3-$ | | L-prolinamide | **3g** | 68 |
| 11 | (1*H*-indol-3-yl)$CH_2$ | H | L-tryptophanamide | **3h** | 75 |
| 12 | *p*-$HOC_6H_4CH_2$ | H | L-tyrosinamide | **3i** | 90 |
| 13 | $CH_3CH(OH)$ | H | L-threoninamide | **3j** | 0 |
| 14 | $HOCH_2$ | H | L-serinamide | **3k** | 0 |

[a] *Reaction conditions:* 2-iodobenzyl bromide (0.5 mmol), amino acid amide (0.75 mmol), CuI (0.05 mmol), $K_2CO_3$ (1 mmol), DMF (5 mL), 110 °C, 24 h.
[b] Isolated yield.
[c] 97% *ee* (*S* form).
[d] 97% *ee* (*S* form).
[e] 96% *ee* (*R* form).

Slight racemization (2% to 3%) also occurred for L- and D-alaninamides during the reaction (entries 3 and 4).

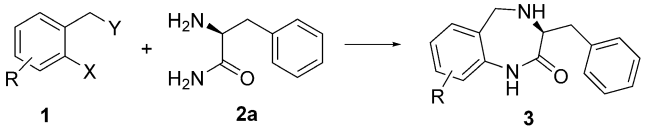
All of the amino acid amides examined afforded moderate to excellent yields (Table 2, entries 1–12). In brief, alaninamide, L-butyrinamide, L-valinamide, L-leucinamide and L-phenylglycinamide all afforded the target products with moderate to high yields (entries 3–12), while the cyclic amino acid amide L-prolinamide also gave a good yield (entry 10).

L-Tryptophanamide with an indolyl group which may participate in C–N coupling reaction produced the target material with 75% yield (entry 11). On the other hand L-tyrosinamide which should have formed a phenolate under the basic conditions, gave a surprisingly high yield of 90%, as shown by the absence or trace of by-product formed during the domino reaction (entry 12).

In contrast to the above, both L-threoninamide and L-serinamide gave no target product due to the strong coordination between copper and this kind of substrate (entries 13 and 14).

Subsequently, *ortho*-halobenzyl halides were examined to react with L-phenylalaninamide under the optimized conditions (Table 3). 2-Iodobenzyl bromide was the best substrate among these *ortho*-halobenzyl halides (entry 1). Surprisingly, unactivated 2-chlorobenzyl halides could also react with L-phenylalaninamide (entries 5–8), and, moreover, they demonstrated nearly the same reactivities as the 2-bromobenzyl halides (entries 5–9 *vs.* 2–4). In general, unactivated chloroarenes are poor substrates for Ullmann C–N

**Table 3.** Domino reaction of various *ortho*-halobenzyl halides and L-phenylalainamide.[a]




1 2a 3

| Entry | R | X | Y | Product | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | H | I | Br | **3a** | 92 |
| 2 | H | Br | Br | **3a** | 87 |
| 3 | 4-$CH_3O$ | Br | Br | **3l** | 82 |
| 4 | 3,4-$OCH_2O$ | Br | Br | **3m** | 47 |
| 5 | 4-F | Cl | Br | **3n** | 89 |
| 6 | 4-$CF_3$ | Cl | Br | **3o** | 82 |
| 7 | 3-Cl | Cl | Br | **3p** | 83 |
| 8 | 3-Cl | Cl | Cl | **3p** | 80 |
| 9 | 4-Cl | Cl | Br | **3q** | 42 |
| 10 | H | F | Cl | **3r** | 0 |

[a] *Reaction conditions: ortho*-halobenzyl halide (0.5 mmol), L-phenylalaninamide (0.75 mmol), CuI (0.05 mmol), $K_2CO_3$ (1 mmol), DMF (5 mL), 110 °C, 24 h.
[b] Isolated yield.

coupling reactions.[15] The reason for the higher reactivity of unactivated 2-chlorobenzyl halides is probably due to the intramolecular coupling reaction.

The reactivity of 2-fluorobenzyl chloride was too low to carry out this domino reaction (entry 10). Two strong electron-donating groups apparently decreased the yield (entry 4), but one methoxy group only marginally influenced the reaction (entry 3). Finally, the low yield of 2-(bromomethyl)-1,4-dichlorobenzene may be caused by the C–N coupling side reaction (entry 9).

In conclusion, a new synthetic method for the Cu-catalyzed domino $S_N2$/coupling reaction has been developed for the synthesis of chiral 3-substituted [1,4]benzodiazepin-2-ones. In the presence of CuI and $K_2CO_3$, amino acid amides and *ortho*-halobenzyl halides were facilely transformed into chiral 3-substituted [1,4]benzodiazepin-2-ones. Moreover the chirality of the chiral amino acid amides was well preserved during the reaction. This synthetic method has some advantages, such as one-pot process, a wide range of substrates, easy operation and cheap copper catalyst. Furthermore, no heavy racemization was observed *via* chiral HPLC analysis.

## Experimental Section

### General Procedure for Synthesis of Chiral 3-Substituted 1,3,4,5-Tetrahydro-2*H*-1,4-benzodiazepin-2-ones

To an oven-dry test tube with a ground joint neck with a magnetic stir bar were added α-amino acid amide (0.75 mmol), 2-halobenzylic halide (0.5 mmol), CuI (0.05 mmol), $K_2CO_3$ (1 mmol) and DMF (5 mL). The test tube was sealed with a rubber sleeve stopper, and then evacuated and refilled with argon for three cycles. The tube was placed an oil bath preheated at 110 °C for 24 h. After being cooled to room temperature, the reaction mixture was quenched with water and subsequently extracted with ethyl acetate (15 mL) for three times. The extract organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum on a rotary evaporator. The resulting residual was purified by silica gel flash column chromatography with the mixed solution of petroleum ether and ethyl acetate (5:1 to 1:1 (v/v)) to give the desired 3-substituted 1,3,4,5-tetrahydrobenzo[*e*][1,4]diazepin-2-one.

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## References

[1] K. T. Olkkola, J. Ahonen, in: *Handbook of experimental pharmacology*, Vol. 182, (Eds.: J. Schüttler, H. Schwilden), Springer-Verlag, Berlin, Heidelberg, **2008**, pp 335–360.
[2] M. H. Bolli, J. Marfurt, C. Grisostomi, C. Boss, C. Binkert, P. Hess, A. Treiber, E. Thorin, K. Morrison, S. Buchmann, D. Bur, H. Ramuz, M. Clozel, W. Fischli, T. Weller, *J. Med. Chem.* **2004**, *47*, 2776–2795.
[3] H. J. Breslin, M. J. Kukla, T. Kromis, H. Cullis, F. De Knaep, R. Pauwels, K. Andries, E. De Clercq, M. A. C. Janssen, P. A. J. Janssen, *Bioorg. Med. Chem.* **1999**, *7*, 2427–2436.
[4] J. K. Mishra, P. Garg, P. Dohare, A. Kumar, M. I. Siddiqi, M. Ray, G. Panda, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1326–1331.
[5] a) J. Y. Lee, I. Im, T. R. Webb, D. McGrath, M.-R. Song, Y.-C. Kim, *Bioorg. Chem.* **2009**, *37*, 90–95; b) I. Im, T. R. Webb, Y.-D. Gong, J.-I. Kim, Y.-C. Kim, *J. Comb. Chem.* **2004**, *6*, 207–213.
[6] Takeda Chemical Industries, Ltd., European Patent EP1591120 A1, **2005**.
[7] O. Kinzel, C. Gege, C. Steeneck, G. Kleymann, T. Hoffmann, (Phenex Pharmaceuticals AG), WO Patent WO2013/64231 A1, **2013**.
[8] J. K. Mishra, G. Panda, *Synthesis* **2005**, 1881–1887.
[9] R. A. Sheldon, *Chem. Commun.* **2008**, 3352–3365.
[10] a) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001–1020; b) A. Behr, A. J. Vorholt, K. A. Ostrowski, T. Seidensticker, *Green Chem.* **2014**, *16*, 982–1006.
[11] For reviews, see: a) Y. Liu, J. P. Wan, *Org. Biomol. Chem.* **2011**, *9*, 6873–6894; b) Q. Liao, X. Yang, C. Xi, *J. Org. Chem.* **2014**, *79*, 8507–8515. For examples, see: c) A. Klapars, S. Parris, K. W. Anderson, S. L. Buchwald, *J. Am. Chem. Soc.* **2004**, *126*, 3529–3533; d) X. Lu, L. Shi, H. Zhang, Y. Jiang, D. Ma, *Tetrahedron* **2010**, *66*, 5714–5718.
[12] a) C. Dai, X. Sun, X. Tu, L. Wu, D. Zhan, Q. Zeng, *Chem. Commun.* **2012**, *48*, 5367–5369; b) X. Sun, X. Tu, C. Dai, X. Zhang, B. Zhang, Q. Zeng, *J. Org. Chem.* **2012**, *77*, 4454–4459; c) J. Dong, Y. Wang, Q. Xiang, X. Lv, W. Weng, Q. Zeng, *Adv. Synth. Catal.* **2013**, *355*, 692–696.
[13] a) H. Wei, T. Li, Y. Zhou, L. Zhou, Q. Zeng, *Synthesis* **2013**, *45*, 3349–3354; b) Q. Zeng, H. Wang, T. Wang, Y. Cai, W. Weng, Y. Zhao, *Adv. Synth. Catal.* **2005**, *347*, 1933–1936.
[14] K. Yasukawa, Y. Asano, *Adv. Synth. Catal.* **2012**, *354*, 3327–3332.
[15] a) K. Kunz, U. Scholz, D. Ganzer, *Synlett* **2003**, 2428–2439; b) F. Monnier, M. Taillefer, *Angew. Chem.* **2009**, *121*, 7088–7105; *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971.

  