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Assembly of *N*-substituted pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones via copper catalyzed aryl amination

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ABSTRACT

Copper-catalyzed amination of *N*-heterocycle derived aryl iodides followed by intramolecular condensative cyclization afforded *N*-substituted pyrrolo[2,1-*c*][1,4]-benzodiazepine-5,11-diones with good yields. By varying primary amines and substituents at aromatic ring of aryl iodides, a wide range of these heterocycles were assembled.

1. Introduction

In recent years, a considerable number of reports[1–7] have revealed that pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-dione (PBD) is an important core structure for pharmaceutical design. The successful examples include compound **1** (Fig. 1) that has growth hormone releasing activity,[1] protein PLK1 inhibitor **2**,[2] ST2806 (**3**) that shows inhibitory activity to myeloid differentiation factor 88,[3] as well as protein thioesterase 1 (APT1) inhibitor **4**.[4] Additionally, PBDs have been used as the key intermediates for synthesis of several natural antibiotics and designed antitumor agents.[8]

Since N-functionalization of PBDs plays a key role to obtain diverse and bioactive derivatives, the development of powerful methods for preparing *N*-substituted PBDs (**A**, Fig. 2) is highly desired. Although direct alkylation of *N*-unsubstituted PBDs (**B**) is the most popular and widely used method for synthesizing *N*-substituted PBDs, it suffers from low yields when less reactive alkylating reagents are used.[3,4,9,10] In some cases special reactions have to be employed to achieve this transformation.[11] On the other hand, methods for elaboration of *N*-unsubstituted PBDs are limited. These tricyclic compounds have often been obtained via a condensation/cyclization process of isatoic anhydrides (**C**) with proline derivatives,[9,12] or a reduction/cyclization process of nitro or azido compounds **D**.[10,13] In these cases multi-step synthesis is generally

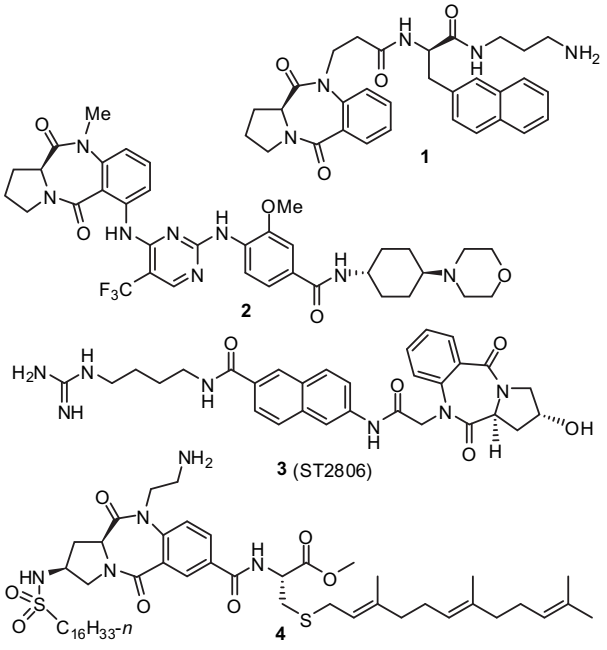

Figure 1. Some representative bioactive molecules with PBD core structure.

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required because some starting materials are not conveniently available (Fig. 2).

During the studies on the synthesis of heterocycles via copper-catalyzed cross-coupling reactions,[14,15] we became interested in aryl amination of aryl halides **E** that possess a proline core linked by an amide bond. We envisaged that after the amination took place, cyclization would occur via an intramolecular amide formation. This approach would offer a diverse and efficient method for assembling *N*-substituted PBDs using primary amines and aryl halides as the starting materials (Fig. 2).

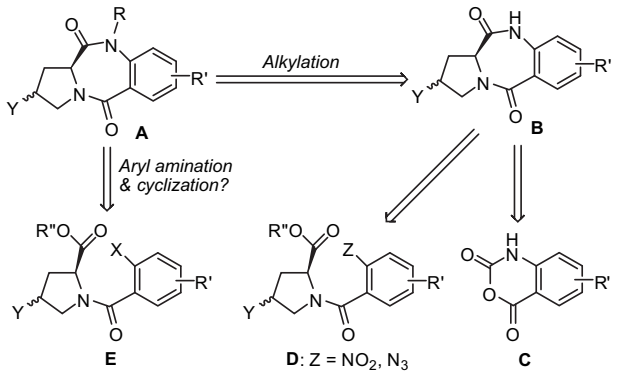
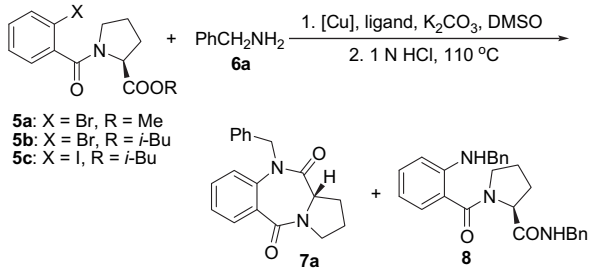


Figure 2. Possible approaches for assembling *N*-substituted PBDs.

2. Results and discussion

With the above idea in mind, a coupling reaction between aryl bromide **5a** and benzylamine was conducted under our typical reaction conditions (10 mol % CuI, 20 mol % L-proline, K_2CO_3, DMSO, 90 °C).[16] It was found that after coupling the desired tricyclic product **7a** was isolated in 52% yield, together with amide **8** in 22% yield (Table 1, entry 1). The formation of **8** should be resulted from the simple condensation of methyl ester **5a** with benzylamine. After failed in inhibiting this side reaction by tuning the reaction conditions (using different bases and copper salts), we moved our attention to employing sterically hindered *i*-butyl ester **5b** as our substrate. This change could inhibit the direct intermolecular condensation with benzylamine. However, after coupling reaction condensative cyclization turned to be slow and the direct coupling product was isolated in 15% yield (entry 2). To solve this problem, we acidified the coupling reaction mixture with 1 N HCl and then heating the solution at 110 °C. In this case **7a** was isolated in 72%

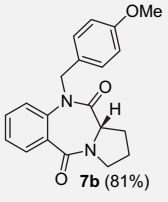
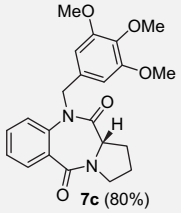
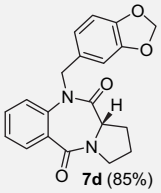
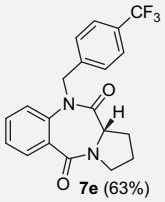
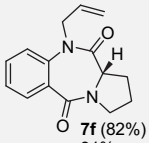
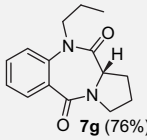
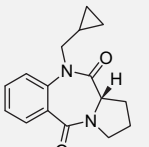
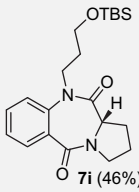
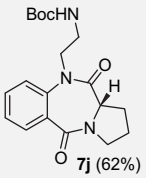
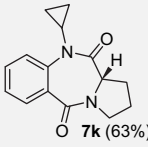
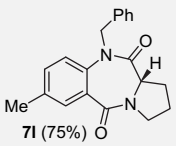
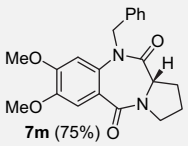
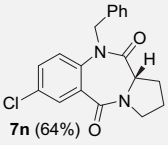
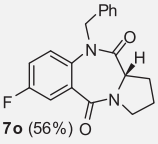
Table 1
Coupling of aryl halides **5** with benzylamine and subsequent cyclization under different conditions[a]



Entry	Substrate	Catalyst[b]	*T* (°C)	Yield of **7a**[c] (%)
1	**5a**	A	90	52[d]
2	**5b**	A	90	55[d]
3	**5b**	A	90	72
4	**5b**	B	90	74 (80% ee)
5	**5c**	B	80	78 (93% ee)

[a] Reaction conditions: aryl halide (1 mmol), benzylamine (2.5 mmol), catalyst (0.1 mmol), K_2CO_3 (2 mmol), DMSO (1 mL), 24 h; then 1 N HCl, 110 °C.
[b] A: CuI/L-proline; B: Pre-synthesized complex by heating a mixture of Cu_2O and L-proline in toluene.
[c] Isolated yield.
[d] The product was directly isolated from coupling reaction mixture, together with **8** in 22% yield (entry 1), or direct coupling product in 15% yield (entry 2).

Table 2
Synthesis of pyrrolo[2,1-*c*][1,4]benzodiazepine-5,11-diones via coupling and subsequent condensation[a]

Entry	Product (yield)[b]	Entry	Product (yield)[b]
1	 **7b** (81%)	2	 **7c** (80%)
3	 **7d** (85%)	4	 **7e** (63%)
5	 **7f** (82%) 91% ee	6	 **7g** (76%) 95% ee
7	 **7h** (70%) 97% ee	8	 **7i** (46%)
9	 **7j** (62%)	10	 **7k** (63%)
11	 **7l** (75%)	12	 **7m** (75%)
13	 **7n** (64%)	14	 **7o** (56%)

[a] Reaction conditions: 2-iodobenzamide (1 mmol), amine (2.5 mmol), catalyst (0.2 mmol, pre-synthesized complex by heating a mixture of Cu_2O and L-proline in toluene), K_2CO_3 (2 mmol), DMSO (1 mL), 80 °C, 24 h; then 1 N HCl, 110 °C for 5 h.
[b] Isolated yield.