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Tandem one pot synthesis of 1,5-benzodiazocine-2-one by isocyanide based Ugi multicomponent reaction

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ABSTRACT

We have developed an efficient one-pot, two-step reaction protocol for the synthesis of eight-membered 1,5-benzodiazocine-2-ones by Ugi four-center three-component coupling reaction (U-4C-3CR) and subsequent reductive cyclization using Fe/NH_4Cl in protic solvent.

Benzofused cyclic molecules play important roles in both drug discovery and chemical biology.[1] In particular, seven and eight membered heterocycles like azocines and diazocines are constituents of a number of compounds with interesting pharmacological properties.[2,3] Benzodiazocines containing two nitrogen atoms are present in various biologically active molecules possessing antihypertensive,[4a] herbicidal,[4b] anti-depressant,[4c] analgesic,[4d] antitussive,[4e] and anthelmintic[4e] activities. Moreover, 1,5-benzodiazocines have attracted much interest as homologs of 1,4-benzodiazepine drugs[5] and inhibitors of 17-β hydroxysteroid dehydrogenase type 3.[6] However, medium sized heterocycles, that is eight or higher membered rings are difficult to prepare due to enthalpic and entropic reasons and transannular interaction.[7] In continuation of our interest in developing expeditious routes to various heterocyclic molecules, we therefore undertook a study to establish a convenient synthetic route to such molecules Scheme 1.

Generating a remarkably high degree of molecular complexity in just one step is among the most challenging objectives in modern organic synthesis. In this context, multicomponent reactions (MCRs)[8] are very relevant because they are extremely convergent, leading to the formation of multiple bonds with a high bond forming efficiency (BFE).[9] While the classical versions of Ugi[10] and Passerini[11] reactions lead to acyclic adducts, we realized that interesting heterocyclic structures may be accessed by their intramolecular variants or by coupling the isocyanide based multi component reaction (IMCR)[12] with a subsequent secondary transformation, taking advantage of additional functionalities suitably placed on one or two of the components.

Transition metals have also been used for catalyzing transformations in tandem[9,13] processes in an attempt to construct biologically active heterocyclic compounds and significant progress has been made in this regard. Cropper et al.[14] tried to construct the eight-membered benzolactam ring using intramolecular Pd-catalyzed aryl amidation reaction, but tandem C–N/C–O bond forming reaction occurred instead, furnishing novel spiro benzofuran lactams. Recently we reported[15] the synthesis of chiral 1,5-benzodiazocine derivatives by Pd catalyzed intramolecular aryl amination reaction using different sugar derived amines. Buchwald and co-workers[16] have reported an interesting approach toward the synthesis of benzofused medium ring heterocycles by aryl amidation followed by β-lactam ring opening reaction. However, the possibility of an easy access to β-lactams[17] via Ugi four-center three-component coupling reaction (U-4C-3CR) encouraged us to construct an intermediate that can provide the 1,5-benzodiazocine skeleton by reductive cyclization accompanied by nucleophilic substitution to open the β-lactam ring. We noted that Andreana and co-workers[18] have synthesized 1,4-benzodiazepinone derivatives employing Ugi reaction and aza-Michael cyclization using Fe/NH_4Cl in ethanol as reducing agent under microwave condition. In this Letter we report an efficient one-pot two-step reaction protocol utilizing Ugi three-component reaction and reductive cyclization using Fe/NH_4Cl, an environmentally benign reagent, to furnish the highly substituted benzofused eight-membered heterocycles Table 1.

In this tandem reaction, the first step is a Ugi multicomponent reaction carried out using different isocyanides, aromatic nitro

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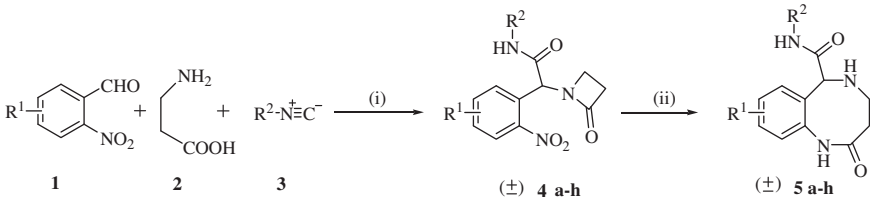


4a/5a, R^1 = 4, 5-OMe, R^2 = Cyclohexyl
4b/5b, R^1 = 4, 5-OMe, R^2 = *tert*-Butyl
4c/5c, R^1 = 4, 5-OMe, R^2 = *iso*-Propyl
4d/5d R^1 = H, R^2 = Cyclohexyl
4e/5e, R^1 = H, R^2 = *tert*-Butyl
4f/5f, R^1 = H, R^2 = *iso*-Propyl
4g/5g, R^1 = 5-Cl, R^2 = Cyclohexyl
4h/5h, R^1 = 4-CF_3, R^2 = Cyclohexyl

Scheme 1. Reagents and conditions, (i) EtOH/H_2O (2:1), rt; (ii) Fe/NH_4Cl, EtOH/H_2O (2:1), 85–100 °C.

Table 1
Optimization experiments for β-lactam ring opening reaction

Entry	Substrate	Reagent	Solvent	Temperature (°C)	Time (h)	Product	Yield (%)
1	**4a**	Fe/NH_4Cl	CH_3CN/H_2O	90	16	**5a**	70
2	**4a**	Fe/NH_4Cl	EtOH/H_2O	100	15	**5a**	81
3	**4a**	Fe/NH_4Cl	MeOH/H_2O	85	16	**5a**	71
4	**4a**	In/NH_4Cl	EtOH/H_2O	100	18	**5a**	68
5	**4b**	In/NH_4Cl	MeOH/H_2O	85	20	**5b**	62
6	**4d**	Fe/NH_4Cl	CH_3CN/H_2O	90	20	**5d**	58
7	**4h**	In/NH_4Cl	EtOH/H_2O	100	18	**5h**	74

Table 2
Synthesis of 1,5-benzodiazocine-2-one using β-alanine as amino acid

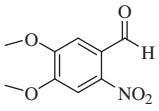
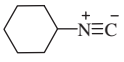
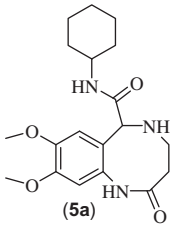
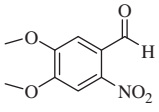
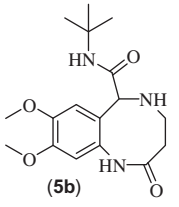
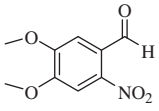
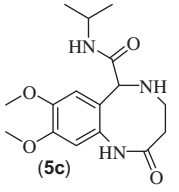
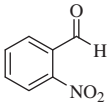
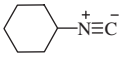
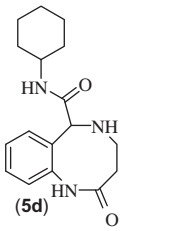
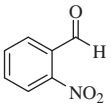
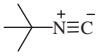
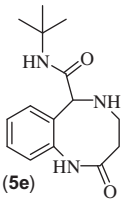
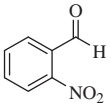
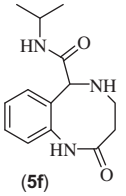
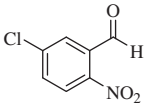
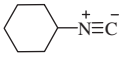
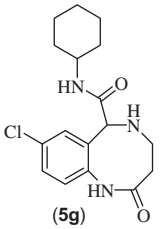
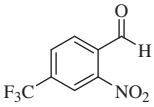
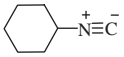
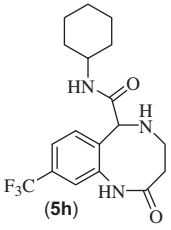
Entry	Nitro aldehyde	Isocyanide	Product	Overall yield (%)
1			 (**5a**)	81
2			 (**5b**)	75
3			 (**5c**)	72
4			 (**5d**)	76

Table 2 (*continued*)

Entry	Nitro aldehyde	Isocyanide	Product	Overall yield (%)
5			 (**5e**)	66
6			 (**5f**)	61
7			 (**5g**)	73
8			 (**5h**)	88

aldehydes, and β-alanine to furnish well established β-lactam products. Among the isocyanides tested *o*-tolyl and 2-naphthyl isocyanides gave only poor yield and were excluded from further studies which were carried out using the three aliphatic isocyanides (i.e., cyclohexyl, *tert*-butyl, and *iso*-propyl). We further planned to reduce the nitro group in the lactam products to aromatic amine in the hope that this group would make a nucleophilic attack on the lactam carbonyl to open the lactam ring. Although *p*-nitro aromatic aldehydes have been employed for the synthesis of β-lactams by Ugi reaction, we used the *o*-nitro isomers to access the eight-membered heterocyclic ring. Among various reagents and solvents tried to reduce the aromatic nitro group, Zn, or Sn in CH_3COOH afforded the aromatic amine but cyclization did not occur. We then came across a publication wherein a six-membered heterocycle (an oxazine) has been synthesized[19] employing In/NH_4Cl in ethanol–water medium for reduction and subsequent β-lactam ring opening reaction. We therefore decided to use this and also the related two-electron reducing agent Fe(0) with NH_4Cl in aqueous medium due to its mild acidic nature and also high functional group tolerance.[20] To our satisfaction, reduction and also cyclization took place rapidly, furnishing medium ring heterocycles. An electron withdrawing group present in the aromatic nitro aldehyde was expected to enhance the rate of both the steps of the reaction. Indeed, the trifluoro methyl substituted nitro aldehyde produced 1,5-benzodiazocine-2-one **5h** in very good yield (88%).[21] The some what higher yield obtained using cyclohexyl isocyanide (Table 2, entry 1 vs 2, 3; 4 vs 5, 6) may be ascribed to the smaller steric size.

In conclusion, we have developed an efficient one-pot, two-step reaction protocol for the synthesis of eight-membered 1,5-benzodiazocine-2-one from readily available aromatic nitro aldehydes **1**, β-alanine **2** and isocyanides **3** by Ugi MCR. Using protic solvent and the two electron reducing agent Fe(0)/NH_4Cl for the reductive cyclization step, these biologically relevant small molecules can be prepared efficiently. Experiments are in progress in our laboratory to effect aryl amination followed by β-lactam ring opening reaction using bromo lactams instead of nitro lactams **4** to get 1,5-benzodiazocine-2-one derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.013.

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21. *General procedure for the preparation of compound* ***5****:* The beta-amino acid (1.2 mmol, 1.2 equiv) and the nitro-aldehyde (1.0 mmol, 1.0 equiv) were dissolved in 20 ml ethanol–water (2:1). The solution was allowed to stand at room temperature for half an hour. The isocyanide (1.0 mmol, 1.0 equiv) was added to the previous solution and the resulting mixture was stirred at room temperature for 20 h, when the reaction appeared complete by TLC (CH_2Cl_2/MeOH 98:2), Fe powder (1 mmol) and solid NH_4Cl (8–10 equiv.) were added. The reaction mixture was stirred at 80 °C for 16 h. Then it was cooled, filtered through a celite pad and extracted with ethyl acetate (3 × 30 mL). The extract was washed with brine (30 mL) and dried (sodium sulphate); the solvent was evaporated to give a crude product. This was purified by column chromatography over silica gel (60–120 mesh) using DCM in 5% methanol as an eluent, when **5a** was isolated as a light yellow solid. Compound **5a**: Yield: 81%, mp 202–204 °C, IR (KBr) ν_{max} = 1517, 1666, 2928, 3073, 3349, 3443 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ_H = 0.08–0.16 (m, 3H), 1.25 (s, 1H), 1.31–1.37 (m, 2H), 1.57–1.59 (m, 1H), 1.65–1.70 (m, 2H), 1.85–1.89 (m, 2H), 2.81–2.85 (m, 1H), 2.98–3.02 (m, 1H), 3.16–3.19 (m, 1H), 3.68–3.70 (m, 1H), 3.77 (s, 3H), 3.83 (s, 3H), 5.40 (s, 1H), 6.07–6.15 (m, 1H), 6.30 (s, 1H), 6.70 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ_C = 22.6 ($2CH_2$), 24.6 (CH_2), 32.6 (CH_2), 32.7 (CH_2), 36.1 (CH_2), 38.9 (CH_2), 48.6 (CH), 55.0 (CH), 55.7 (CH_3), 56.5 (CH_3), 101.1 (CH), 111.1 (C), 112.0 (CH), 139.3 (C), 142.0 (C), 150.1 (C), 168.0 (C), 168.8 (C) ppm; MS (ESI): m/z = 384 $[M+Na]^+$. Anal. Calcd for $C_{19}H_{27}N_3O_4$: C, 63.14; H, 7.53; N, 11.63. Found: C, 63.27; H, 7.61; N, 11.52.