A One-Pot Isocyanide-Based Five-Component Reaction: Synthesis of Highly Functionalized *N*-Cyclohexyl-2-(2,4-Dioxo-2,3,4,5 Tetrahydro-1*H*-Benzo[b][1,5]Diazepin-3-yl)-2-Phenylacetamides

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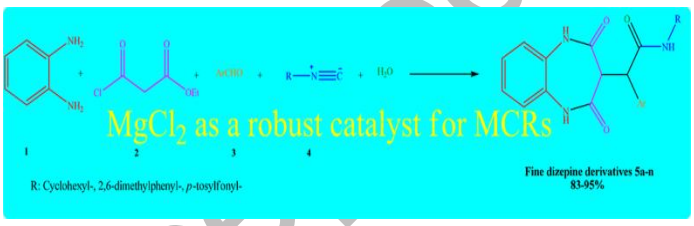
Abstract

A new protocol has been developed for the efficient synthesis of structurally diverse *N*-cyclohexyl-2-(2,4-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[b][1,5]diazepin-3-yl)-2-phenylacetamides *via* a one-pot, five-component condensation reaction of an aromatic diamine, an aromatic aldehyde, an isocyanide, ethyl malonyl chloride, and water in dichloromethane with good yields, at ambient temperature, in the presence of $MgCl_2$ as a catalyst.

Graphical Abstract



KEYWORDS: Diazepine, Multi-component reaction, Isocyanide.

INTRODUCTION

One of the most important challenges in pharmaceutical chemistry is the design and synthesis of biologically active molecules. Multi-component reactions (MCRs) are potent transformations and very effective synthetic routes in which three or more starting

materials are combined in a one-pot fashion to reach highly garnished products. These methods have considerable advantages over the classical stepwise procedure permitting some chemical bonds formation and making complex molecular structures from routinely and in particular simple precursors in an only one synthetic workup without isolation of intermediates from the reaction mixture [1–3]. MCRs, specially isocyanide based multi-component reactions (IMCRs) are considered as potent ones in drug discovery and high-throughput synthesis of organic compounds [4]. The pharmaceutical industry has focused on diversity-oriented and biased combinatorial libraries [5]. Recently, design of multi-component reactions (MCRs) with high atom economy, high conversion character, and facility in a one-pot form has achieved noticeable interest because of their capability to produce more molecular variety and complexity [6–8].

Synthesis and use of different types of benzodiazepines as an important class of heterocycles have been reported in the literature [9–12]. Recently, the area of biological interest of benzodiazepines has been extended to antibiotics [13–17]. Also, they are extensively investigated for therapeutic applications such as development of anxiolytic and antipsychotics agents [18, 19], antiarrhythmics [20], drags to treat viral infection (HIV) [21, 22], cholecystokinin-B receptor antagonists [23, 24] and cardiovascular disorders [25]. In addition, these heterocycles have prominent anticonvulsant properties which are considered in epilepsy treatment [26, 27]. Benzodiazepines have the privilege to be privileged the scaffold [28–37] certainly in the core of many compounds, including peptide hormones such as Cholecystokinin(**A**) [38] potassium blockers (**B**) [36, 39] and interleukin-1B converting enzyme (ICE) inhibitor (**C**) [40] (Fig. 1). In addition, Ursini and co-workers

reported that 3-(aryloxycarbonyl)amino-2,4-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine **D** acts as a cholecystokinin-*B* receptor antagonists [41]. A literature survey shows that there is a large number of reports on the synthesis of benzodiazepine derivatives [42]. Lately, Shaabani et al. reported a synthetic pathway for benzo[b][1,5]diazepine-2,4-diones whose structures are nearly similar to the compounds in this work [24]. Li group using this method reported a new type of anticancer agent [43]. In addition, Bazgir using Meldrum's acid *via* a two different multi-component reactions synthesized the title compound [44, 45].

In line of our previous studies on IMCRs [46–49], we wish to highlight our findings about synthesis of highly functionalized *N*-cyclohexyl-2-(2,4-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[b][1,5]diazepin-3-yl)-2-phenylacetamides **5a-n** *via* a one-pot five-IMCR of benzene-1,2-diamine **1**, ethyl malonyl chloride **2**, benzaldehyde **3**, isocyanide **4** and water in dichloromethane at room temperature, in the presence of $MgCl_2$ as catalyst (Scheme 1).One of the drawbacks of the previously described methods for the synthesis of diazepins was the long reaction times [44]. Using **2** instead of Meldrum's acid and $MgCl_2$ as catalyst, high number of different chemicals was synthesized.

DISCUSSION

To optimize the conditions for the synthesis of *N*-cyclohexyl-2-(2,4-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[b][1,5]diazepin-3-yl)-2-phenylacetamides, **1**, **2**, 4-fluorobenzaldehyde, cyclohexyl isocyanide and water were selected as model reactants. Firstly, the effect of various solvents were evaluated (Table1). As can be seen in Table 1,

the results showed that the efficiency and the yield of the reaction in CH_2Cl_2 was higher than those obtained using other solvents.

As indicated in Table 2, the reaction of **1**, **2**, 4-fluorobenzaldehyde, cyclohexyl isocyanide and water was also carried out in the presence of various acidic and basic catalysts (40 mol%). Results showed that reaction proceeds in the presence of both series of catalysts and higher reaction yield was reached using $MgCl_2$. Subsequently, testing the effect of catalyst loading with values of 10, 20, 30, and 40 mol % was carried out. The results indicated that 20 mol % of catalyst was optimal. Higher amounts of catalyst did not lead to a significant change in yield. We continued to focus on the optimization of reaction conditions. Initially, this transformation was carried out in dichloromethane at room temperature in the absence of catalyst. It was found that the yield of product was low even after 24 h (entry 1, Table 2). To increase yield of reaction, 40 mol % of catalyst was added to the reaction system. The results are summarized in Table 2. Among them, $MgCl_2$ was proven superior to other catalyst, and the yield of the desired product **5a** could be increased to 93% (entry 1, Table 3). As shown in Table 3, the both electron-withdrawing and electron-donating benzaldehydes were examined and the reaction proceeded with both of them.

In the next step, this promising reaction was further synthesized through varying the structure of the isocyanide component (Table 3). The reaction proceeds under mild conditions at room temperature in a manner that no undesirable side reaction and products were observed.

A possible mechanism for the formation of product **5a** is shown in Scheme **2**. It is conceivable that the initial event is the formation of intermediate **6** through nucleophilic attack of benzene-1,2-diamine **1** to acyl portion of ethyl malonyl chloride **2**. Then, an intermolecular cyclization of **6** affords seven-membered ring **7** in the presence of a catalytic amount $MgCl_2$. Knoevenagel condensation reaction of **3** and **7** in the presence of $MgCl_2$ after passing some steps leads to α,β-unsaturated molecule **10** [44, 45]. On the basis of the well-established chemistry of reaction of Michael-type addition reaction of an isocyanides **4** with α,β-unsaturated compound **10** [50, 51], intermediate **11** was produced by nucleophilic attack of isocyanide **4** to α,β-unsaturated compound **10** using catalyst followed by nucleophilic attack of a H_2O molecule on the nitrilium moiety and production of compound **13**. Finally, after two tautomerizations of intermediate **13** the diazepine- amide **5a** is produced.

CONCLUSIONS

In summary, an impressive and simple procedure to construct the highly functionalized benzo[b][1,5]diazepin scaffolds from readily available starting materials was developed. This effective strategy for the preparation of synthetically, pharmaceutically and biologically interesting benzodiazepine derivatives includes some important features like the mild reaction conditions, excellent yields, high atom economy, and easy workup procedure.

EXPERIMENTAL

General

All chemicals and reagents were purchased from Across, Alfa Aesar, Daejung or Merck chemical companies and were used without purification. The identify of previously known organic products were confirmed through comparison of their melting points and ^{1}H NMR spectral data with those reported in the literature [44, 45]. Structure of other synthetic compounds were elucidated using IR, 1H NMR, 13C NMR spectroscopy and the elemental analysis. Melting points were determined on a Buchi B-545 apparatus using open capillary tubes. The reactions was monitored by TLC using silica gel SIL G/UV 254 plates. FT-IR spectra were recorded as KBr pellets using a Shimadzu Corporation spectrometer at 400–4000 cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance DPX FT-NMR spectrometer at 400 and 100 MHz, respectively (δ in ppm). EI-MS (70 eV): Finningan-MAT-8430 mass spectrometer; in m/z. Elemental analyses were performed using a Heraeus CHNS Rapid analyzer.

General Procedure For The Synthesis (5a-N) Using One-Pot Five Component Method

A solution containing **1** (1 mmol), **2** (1 mmol), benzaldehyde (1 mmol), isocyanide (1 mmol), H_2O (0.5 mL) and $MgCl_2$ (0.2 mmol) in CH_2Cl_2 (5 mL) was stirred for 5 h at room temperature. After completion of the reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 1/1), the reaction solution was filtered off and the residue was washed several time with EtOH to receive **5a-n**.

Spectral Data Of *N*-Cyclohexyl-2-(2,4-Dioxo-2,3,4,5-Tetrahydro-1*H*-Benzo[B][1,5]Diazepin-3-Yl)-2-(4-Fluorophenyl)Acetamide (5a):

Yield 93%. White powder; mp 261-263°C; IR (KBr, cm^{-1}) 3323, 3176, 3071, 2983, 2930, 2855,1700, 1641, 1590, 1546, 1509, 1427, 1327, 1256, 1146, 1084. ^{1}H NMR (300.13 MHz, DMSO-d_6) δ=0.97 – 1.77 (m, 5CH2 of cyclohexyl); 3.39 (br. s, CH of cyclohexyl, overlap with solvent); 3.76 (d, J=11.2, CH); 4.38 (d, J=11.2, CH); 6.99 – 7.24 (m, 8 arom. H); 8.10 (d, J=7.2, NH_ cyclohexyl); 10.36 (s, NH); 10.55 (s, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ:24.28, 24.34, 25.14, 31.82, 32.25, 47.35, 51.38, 113.20, 113.41, 114.92, 115.14, 122.33, 123.62, 125.19, 125.27, 129.79, 141.80, 160.40, 162.81, 164.20 ppm. -).Anal. calc. for $C_{23}H_{24}FN_3O_3$(409.18): C 67.47, H 5.91, N 10.26; found: C 67.81, H 5.97, N 9.99.

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"Supporting Information: Full experimental detail, spectra data and copies of ^{1}H NMR and ^{13}C NMR spectra of **5a, 5f** and **5h** and Copies of ^{1}H NMR spectra of known compounds can be found via the "Supplementary Material" section of this article's webpage."

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Table 1. Effect of solvent on the model reaction[a]

Entry	Solvent	Time(h)	Yield[b](%)
1	MeCN	10	65
2	EtOAc	15	52
3	Toluene	12	27
4	EtOH	12	15
5	CH_2Cl_2	8	93

[a]Benzene-1,2-diamine (1 mmol), ethyl malonyl chloride (1 mmol), 4-fluorobenzaldehyde (1 mmol), cyclohexyl isocyanide (1 mmol) and water(1 mmol) at room temperature, in the presence of $MgCl_2$ (20 mol %).

[b]Isolated yield

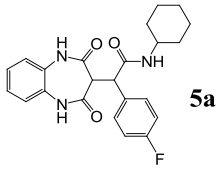
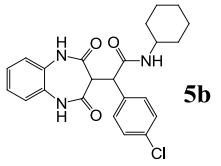
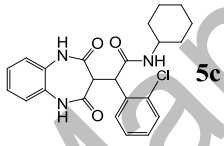
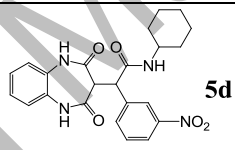
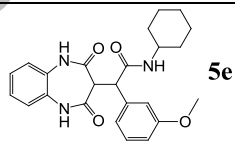
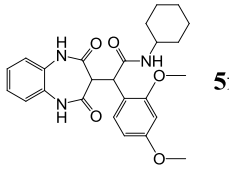
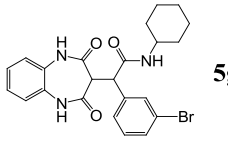
Table 2. Monitoring of the catalyst effect and catalyst amount on the model reaction[a]

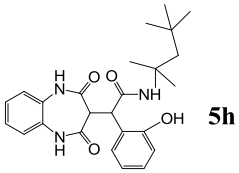
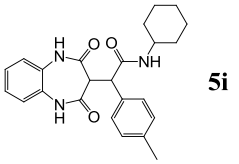
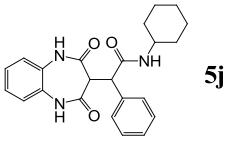
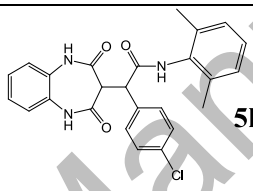
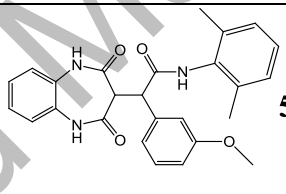
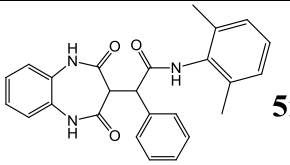
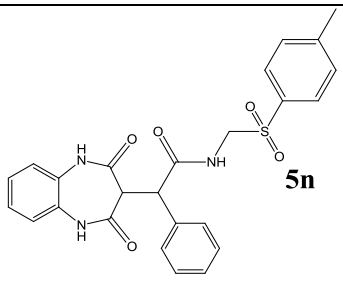
Entry	Catalyst	Time(h)	Yield[b](%)	Catalyst amount (mol%)
1	-	24	18	40
2	Na_2CO_3	12	25	40
3	$NaHCO_3$	12	27	40
4	Pyridine	12	22	40
5	NaH	12	65	40
6	Et_3N	12	25	40
7	$NiCl_2$	12	30	40
8	$[bmim]_5[PW_{11}ZnO_{39}].3H_2O$	12	21	40
9	$H_6[P_2W_{18}O_{62}].18H_2O$	12	20	40
9	$MgBr_2$	12	72	40
10	$MgCl_2$	6	93	20

[a]Benzene-1,2-diamine (1 mmol) , ethyl malonyl chloride (1 mmol), 4-fluorobenzaldehyde (1 mmol), cyclohexyl isocyanide (1 mmol) and water(1 mmol) at room temperature, in the presence of catalyst

[b] Isolated yield

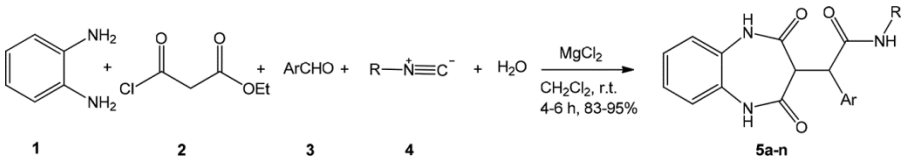
Table 3. Synthesis of diazepine in the presence of $MgCl_2$

Entry	Aryl aldehyde	Isocyanide	Product	Time(h)	Yield[b](%)
1	4-F-C_6H_4	Cyclohexyl	 **5a**	5	93
2	4-Cl-C_6H_4	cyclohexyl	 **5b**	4	89
3	2-Cl-C_6H_4	cyclohexyl	 **5c**	6	91
4	3-NO_2-C_6H_4	Cyclohexyl	 **5d**	5	95
5	3-MeO-C_6H_4	Cyclohexyl	 **5e**	5	89
6	2,4-diMeO-C_6H_4	Cyclohexyl	 **5f**	6	87
7	3-Br-C_6H_4	Cyclohexyl	 **5g**	5	91

8	2-OH-C_6H_4	1,1,3,3-tetramethylbutyl	 **5h**	5	93
9	4-Me-C_6H_4	Cyclohexyl	 **5i**	6	85
10	Ph	Cyclohexyl	 **5j**	6	84
11	4-Cl-C_6H_4	2,6-$Me_2C_6H_3$	 **5k**	6	86
12	3-MeO-C6H4	2,6-$Me_2C_6H_3$	 **5l**	4	92
13	Ph	2,6-$Me_2C_6H_3$	 **5m**	6	88
14	Ph	4-Me-C_6H_4-SO_2CH_2	 **5n**	6	80

[a]Isolated yield.

Scheme 1. Synthesis of diazepine in the presence of $MgCl_2$ as catalyst



R: Cyclohexyl-, 2,6-dimethylphenyl-, *p*-tosylfonyl-

Scheme 2. Possible mechanism for the formation of product **5a**.

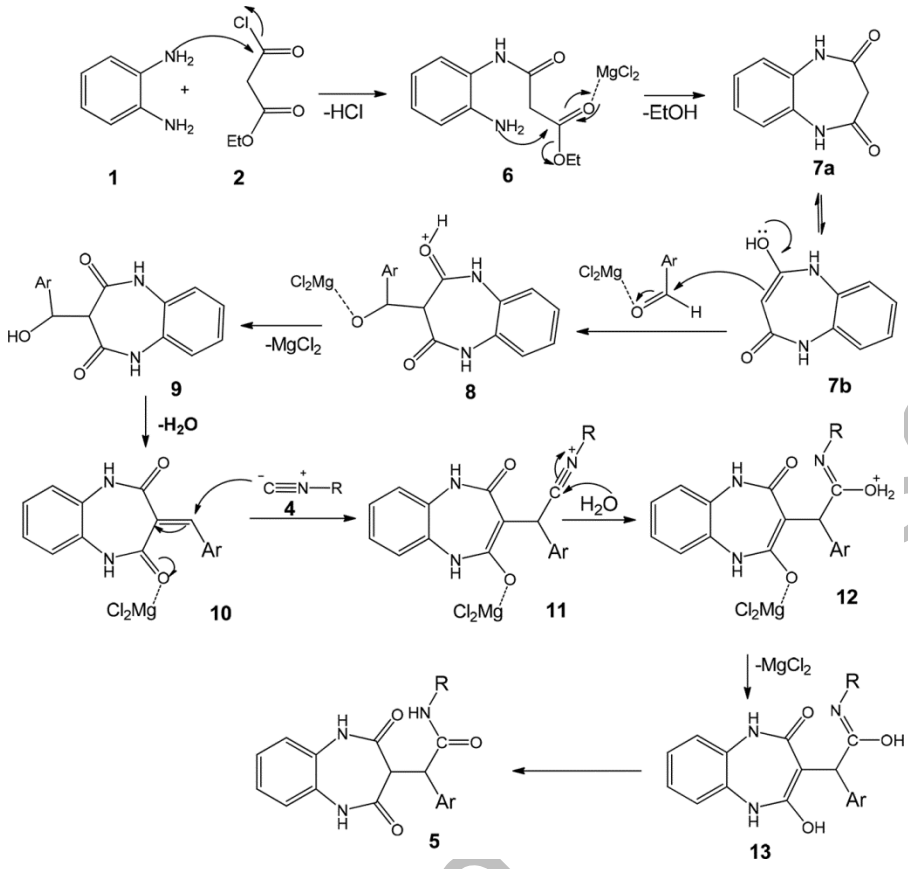


Fig. 1. The structure of some medicinally and biologically important diazepines