Novel Isocyanide-Based One-Pot Multicomponent Syntheses of Tetrahydrobenzo[*b*][1,4]oxazepine and Malonamide Derivatives

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Received October 25, 2009

In this work, a novel one-pot multicomponent reaction of 2-aminophenols, Meldrum's acid, and isocyanides leads to the synthesis of tetrahydrobenzo[*b*][1,4]oxazepine or malonamide derivatives using 1 or 2 equiv of 2-aminophenols, respectively, in good to excellent yields at ambient temperature.

Multicomponent reactions (MCRs) especially isocyanide-based MCRs (IMCRs) are fast and selective methods for the synthesis of large libraries of organic molecules by simply varying each component through a chain of consecutive elementary transformations.[1]

Benzoxazepine derivatives are important scaffolds in medicinal chemistry with various biological activities,[2] and attractive compounds of growing pharmaceutical interest as documented by many publications. Among compounds containing this fragment are a non-nucleoside HIV-1 reverse transcriptase inhibitor,[3] a histamine receptor agonist[4] and calcium antagonists,[5] as well as antidepressants[6] and analgesics.[7] The benzo[*b*][1,4]oxazepine derivatives demonstrate various forms of bioactivity such as antidepressive and anxiolytic activity,[8] treating of bronchial asthma and allergic bronchitis,[9] antiserotoninergic and antihistaminic effects,[10] and tetrahydrobenzo[*b*][1,4]oxazepines are progesterone receptor agonists,[11] and anticancer activity against breast cancer cells.[12]

Malonamide derivatives are of great interest in various respects because of their interesting applications in diverse fields.[13] Malonamide derivatives have some important applications such as excellent ionophores for the construction of alkali and alkaline-earth cations-selective electrodes,[14] effective liquid−liquid extractants for the separation of actinide ions from acid media,[15] as an alternative to carbamoylmethylphosphine oxide (CMPO) systems in the nuclear waste management process, as bidentate chelates especially for uranium(VI) and plutonium(IV) ions,[16] as monomers in the nylons' family and as components in peptidomimetic substances.[17]

In view of our current studies on IMCRs,[18] and a full account of the our previous results,[18g] herein, we describe the synthesis of tetrahydrobenzo[*b*][1,4]oxazepines **4a**−**e** and malonamide derivatives **5a**−**f** via a condensation reaction between an isocyanide **1**, Meldrum's acid **2**, and 1 or 2 equiv of 2-aminophenol **3**, in good to excellent yields at ambient temperature (Scheme 1).

In a pilot experiment, the treatment of cyclohexyl isocyanide, Meldrum's acid, and 2-aminophenol afforded *N*-cyclohexyl-2-methyl-2-(7-methyl-2,4-dioxo-2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepin-3-yl)propanamide **4a** in 87% yield. In the same manner, various 2-aminophenols and isocyanides were coupled with Meldrum's acid in a one-pot operation at room temperature in CH_2Cl_2 to give the corresponding tetrahydrobenzo[*b*][1,4]oxazepine derivatives **4a**−**e** in good to excellent yields.

This method does not require any catalyst for the promotion of the reaction, and undesired side product was not observed. The results shown in Table 1 clearly indicate the scope and generality of the reaction with respect to various starting materials. The reaction proceeds under mild conditions and is compatible with some functional groups. Two substituents in the products can be varied independently of each other.

As shown in Scheme 1, using 2 equiv of 2-aminophenols **3** in the reaction with isocyanide **1** and Meldrum's acid **2**, malonamide derivatives **5a**−**f** were produced via a novel one-pot pseudo five-component reaction under the same reaction conditions in CH_2Cl_2 at room temperature.

The results shown in Table 2 clearly indicate the efficient scope and limitations of this reaction. Also, similar to the previous reaction, this method does not require any catalyst for the promotion of the reaction, and no undesired side product was observed.

Table 1. Synthesis of Tetrahydrobenzo[*b*][1,4]oxazepine Derivatives **4a**−**e**

entry	R^1	R^2	product	yield[a] (%)
1	cyclohexyl	H	**4a**	87
2	cyclohexyl	4-Cl	**4b**	80
3	*tert*-butyl	H	**4c**	80
4	*tert*-butyl	4-CH_3	**4d**	80
5	1,1,3,3-tetramethylbutyl	H	**4e**	75

[a] Isolated yield.

Table 2. Synthesis of Malonamide Derivatives **5a**−**f**

entry	R^1	R^2	product	yield[a] (%)
1	cyclohexyl	4-CH_3	**5a**	87
2	1,1,3,3-tetramethylbutyl	4-CH_3	**5b**	80
3	2,6-dimethylphenyl	H	**5c**	84
4	2,6-dimethylphenyl	4-CH_3	**5d**	82
5	4-methylphenylsulfonyl	H	**5e**	80
6	4-methylphenylsulfonyl	4-CH_3	**5f**	78

[a] Isolated yield.

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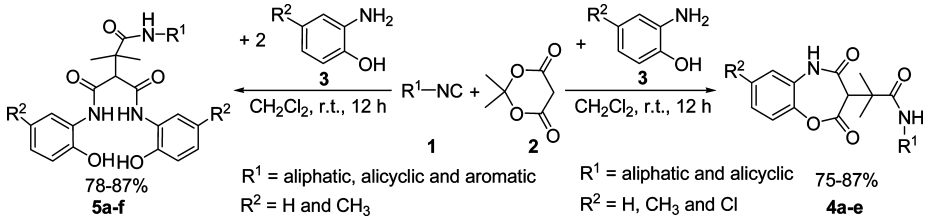
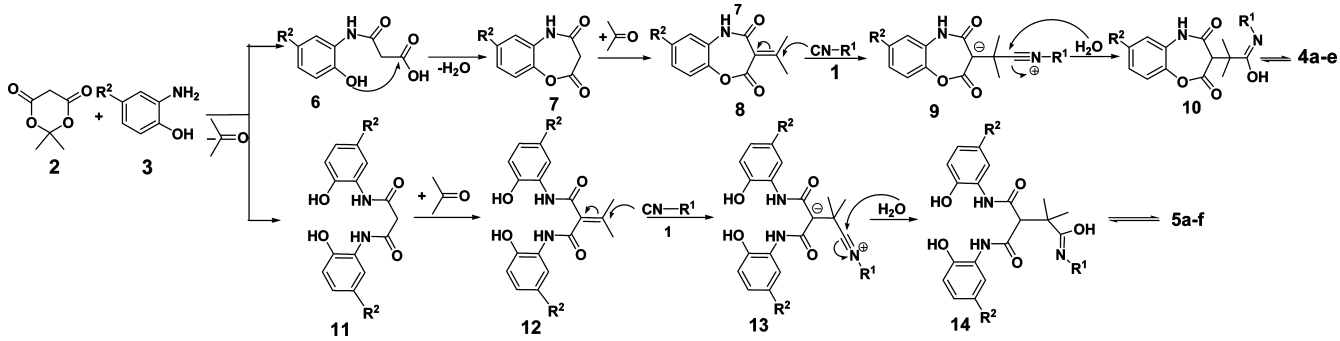
10.1021/cc100032d
Published on Web 07/27/2010

Scheme 1. Synthesis of Tetrahydrobenzo[*b*][1,4]oxazepines **4a**−**e** and Malonamide Derivatives **5a**−**f**



Scheme 2. Possible Mechanism for the Formation of Products **4a**−**e** and **5a**−**f**



The suggested mechanism for the formation of products **4a**−**e** and **5a**−**f** is shown in Scheme 2. It is conceivable that, the initial event is the formation of intermediate **7** or **11** from condensation between a Meldrum's acid **2** and one or two molecules of 2-aminophenol **3** and releasing a molecule of acetone, respectively.[19] Intermediate **7** or **11** undergoes a Knoevenagel condensation reaction with acetone to produce intermediate **8** or **12**, respectively.[20] On the basis of the well-established chemistry of reaction of isocyanides with electron deficient α,*β*-unsaturated carbonyl compounds,[21] intermediate **9** or **13** was produced by nucleophilic attack of an isocyanide **1** to intermediate **8** or **12**, followed by nucleophilic attack of an H_2O molecule on the activated nitrilium moiety to produce compound **10** or **14**. Finally, tautomerization of compound **10** or **14** leads to the formation of products **4a**−**e** or **5a**−**f**.

Conclusions

In summary, we have developed a mild and straightforward procedure for the synthesis of a new class of substituted malonamide and tetrahydrobenzo[*b*][1,4]oxazepine derivatives from a novel IMCR between isocyanides, Meldrum's acid, and 2-aminophenols in CH_2Cl_2 in good to excellent yields at room temperature. In this reaction, for the first time, some potentially excellent ionophores have been reported that can be applied for the construction of alkali and alkaline-earth cations-selective electrodes that can be applied in medicinal chemistry. In other words, this reaction can be regarded as an efficient approach for the synthesis of malonamide derivatives as effective liquid−liquid extractants and tetrahydrobenzo[*b*][1,4]oxazepine derivatives as effective pharmaceutical compounds with various biological activities.

Experimental Section

Melting points were measured on an Electrothermal 9200 apparatus. Mass spectra were recorded on a Shimadzu GCMS-QP1100EX mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. The ^{1}H and ^{13}C NMR Spectra were recorded on a Bruker DRX-300 Avance spectrometer 300.13 and 75.47 MHz. NMR spectrum were obtained on solution in DMSO-d_6 using TMS as internal standard. The chemicals used in this work were purchased from the Merck and Fluka Chemical Companies.

General Procedure for the Preparation of Tetrahydrobenzo[*b*][1,4]oxazepines 4a−f. A mixture of an isocyanide (1 mmol), Meldrum's acid (1 mmol), and a 2-aminophenol (1 mmol) in 3 mL of CH_2Cl_2 was stirred for 12 h at room temperature. After completion of reaction, as indicated by thin-layer chromatography (TLC; ethyl acetate/*n*-hexane, 1/1), the reaction mixture was filtered, and the solid precipitate washed with *n*-hexane (5 mL). Further purification was followed by crystallization from ethanol to give pure crystalline products **4a**−**f**.

General Procedure for the Preparation of Malonamides 5a−f. A mixture of an isocyanide (1 mmol), Meldrum's acid (1 mmol), and a 2-aminophenol (2 mmol) in 3 mL of CH_2Cl_2 was stirred for 12 h at room temperature. After completion of reaction, as indicated by TLC (ethyl acetate/*n*-hexane, 1/1), the reaction mixture was filtered, and the solid precipitate washed with *n*-hexane (5 mL). Further purification was followed by crystallization from ethanol to give pure crystalline products **5a**−**f**.

Acknowledgment. We gratefully acknowledge financial support from the Research Council of Shahid Beheshti University.

Supporting Information Available. Experimental procedures, Mass, IR, ^{1}H NMR, and ^{13}C NMR spectra for compounds **4a**−**e** and **5a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC100032D