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Novel Isocyanide-Based Four-Component Reaction: A Facile Synthesis of Fully Substituted 3,4-Dihydrocoumarin Derivatives

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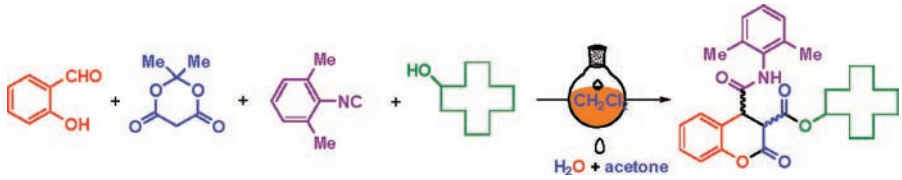
ABSTRACT



A novel isocyanide-based four-component reaction between a 2-hydroxybenzaldehyde, Meldrum's acid, an isocyanide, and an aromatic or an aliphatic alcohol efficiently provide 3,4-dihydrocoumarin derivatives in good to excellent yields without using any catalyst or activation. The reaction can be carried out as a simple one-pot protocol at room temperature.

The 3,4-dihydrocoumarin system is widely distributed in nature,[1] and some derivatives have shown a wide range of biological activities[2] such as aldose reductase inhibition,[3] antiherpetic,[4] protein kinases,[5] and a moderate estrogenic activity.

The most common method for the synthesis of dihydrocoumarins involves (i) the hydroarylation[6] of cinnamic acids with phenols in strong acidic media,[7] (ii) the catalytic hydrogenation of coumarins,[8] (iii) Lewis acid mediated reaction of highly activated phenols with acrylonitrile,[9] and (iv) reaction of chromium Fisher carbene complexes with ketene acetals.[10] However, many of these methods suffer from disadvantages such as lack of substrate generality and the use of a large excess of expensive transition metals catalyst such as $Pd(OAc)_2$,[6a,7f] $Y(OTf)_3$,[11] Ru(III),[12] and $Cr(CO)_5$[3] or corrosive organic acid such as CF_3COOH[7a] and

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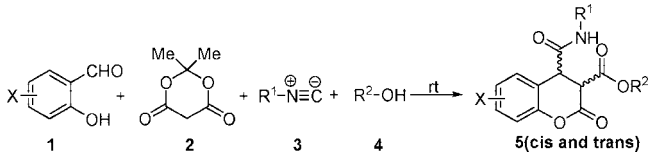
require severe reaction conditions. Recently, Fillion and co-workers reported the synthesis of 3,4-dihydrocoumarins from the reaction of phenols with 5-alkylidine Meldrum's acids in the presence of $Yb(OTf)_3$.[13] However, this method suffers from expensive catalyst, a laborious multistep procedure, and a high reaction temperature.

Multicomponent reactions (MCRs) are special types of synthetically useful organic reactions in which three or more different starting materials react to a final product in a one-pot procedure.[14] Such reactions are atom-efficient processes by incorporating the essential parts of the starting materials into the final product. MCRs are powerful tools in the modern drug discovery process and allow the fast, automated, and high-throughput generation of organic compounds.[15] In the past years the pharmaceutical industry has focused more and more on diversity-oriented and biased combinatorial libraries.[16] Furthermore, the discovery of novel MCRs can be considers as an interesting topic for academic research that also satisfies a practical interest of applied science.[17]

Due to above-mentioned reasons and as a part of our ongoing research program on the isocyanide-based MCRs,[18] here we report synthesis of fully substituted 3,4-dihydrocoumarin derivatives **5** by a four-component condensation reaction of 2-hydroxybenzaldehydes, **1**, Meldrum's acid, **2**, and alkyl or aryl isocyanides, **3**, in the presence of aromatic or aliphatic alcohols, **4** at room temperature (Scheme 1). It

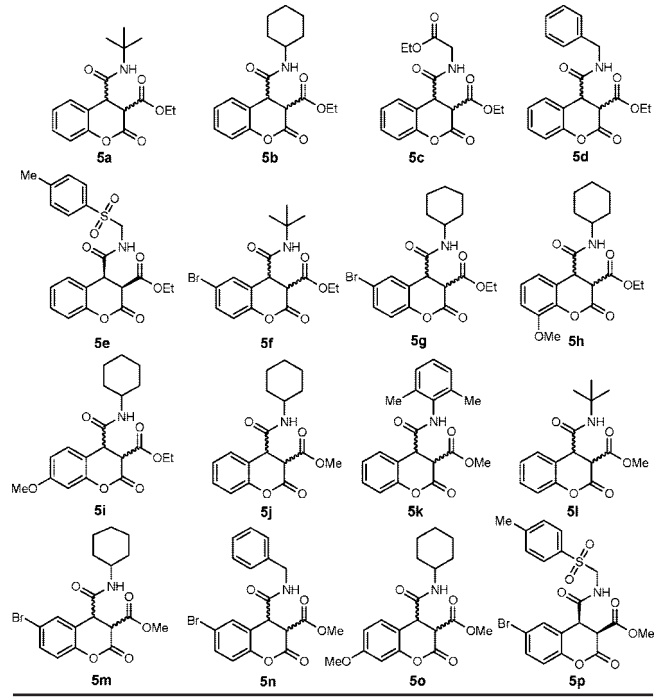
Scheme 1. Synthesis of 3,4-Dihydrocoumarin Derivatives



is worth mentioning that in the course of our reaction, two C−C bonds and several heteroatom−C bonds are newly formed, whereas in the Ugi four-component reaction only one C−C bond and several heteroatom−C bonds are formed. On the other hand, in the present reaction one amide, one ester bond, and a lactose ring are newly formed, while in the Ugi four-component reaction only two amide bonds are formed.

The reaction did not require any optimization. As indicated in Table 1, treatment of various alkyl and aryl isocyanides

Table 1. Synthesis of 3,4-Dihydrocoumarins from 2-Hydroxybenzaldehydes, Meldrum's Acid, and Isocyanides in the Presence of Ethanol or Methanol



R^1	R^2	X	product	yield (%) (cis/trans)
tert-butyl	Et	H	**5a**	85 (76:24)
cyclohexyl	Et	H	**5b**	92 (70:30)
ethylacetate	Et	H	**5c**	75 (72:28)
benzyl	Et	H	**5d**	85 (66:34)
4-tolune-methylsulfonyl	Et	H	**5e**	70 (100:00)
tert-butyl	Et	5-Br	**5f**	82 (66:34)
cyclohexyl	Et	5-Br	**5g**	96 (71:29)
cyclohexyl	Et	3-MeO	**5h**	96 (74:26)
cyclohexyl	Et	4-MeO	**5i**	95 (75:25)
cyclohexyl	Me	H	**5j**	91 (67:33)
2,6-dimethyl-phenyl	Me	H	**5k**	72 (54:46)
tert-butyl	Me	H	**5l**	90 (67:33)
cyclohexyl	Me	5-Br	**5m**	90 (65:35)
benzyl	Me	5-Br	**5n**	82 (61:39)
cyclohexyl	Me	4-MeO	**5o**	90 (74:26)
4-tolune-methylsulfonyl	Me	5-Br	**5p**	80 (100:00)

and various 2-hydroxybenzaldehydes with Meldrum's acid in the presence of ethanol or methanol at room temperature led to the formation of the corresponding fully substituted 3,4-dihydrocoumarin derivatives in excellent yields. The structures of the products **5a**−**p** were deduced from their

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IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values. Finally, the structure of **5a** was confirmed unambiguously by single-crystal X-ray analysis (Figure 1).

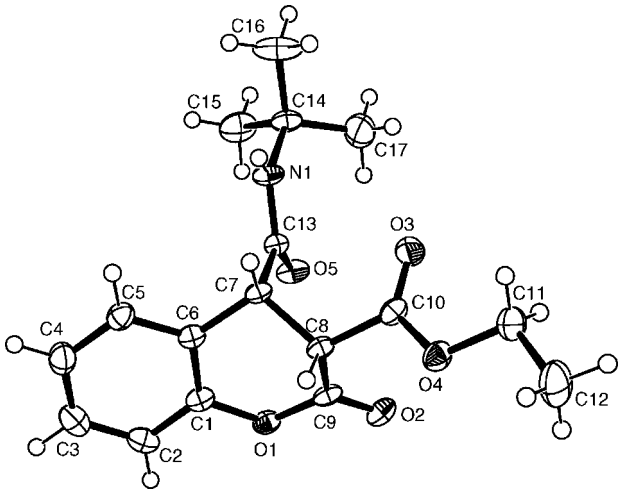


Figure 1. ORTEP diagram for **5a**.

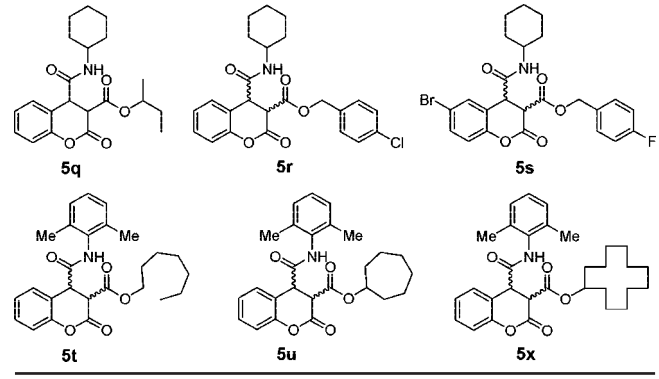
To explore the scope and limitations of this versatile reaction, we have examined various aromatic and aliphatic alcohols in the presence of 2-hydroxybenzaldehyde derivatives, Meldrum's acid, and aromatic and aliphatic isocyanide in dichloromethane at room temperature. As indicated Table 2, the reactions proceed efficiently and led to 3,4-dihydrocoumarin derivatives **5q**−**x** in good yields.

The classical methods for the synthesis of 3,4-dihydrocoumarin involves Michael-type reaction of electron-rich hydroxyarenes with cinnamic acids. Unfortunately, this method is limited to the reaction of cinnamic acids bearing electron-donating groups on the aromatic ring. It is noteworthy that in this method, we were able to synthesize 3,4-dihydrocoumarin with both electron-withdrawing and electron-donating groups on the aromatic ring of the 3,4-dihydrocoumarin system.

It is interesting to note, when the reaction of 4-chlorobenzylalcohol **6** with 2-hydroxybenzaldehyde, Meldrum's acid, and cyclohexyl isocyanide was carried out in excess ethanol, we only obtained product **5b** selectivly, without formation of **5r** (Scheme 2).

It is important to note that compound **5** has two stereogenic centers, and therefore, two pairs of diastereoisomers are expected. The ^{1}H NMR and ^{13}C NMR spectra of the crude

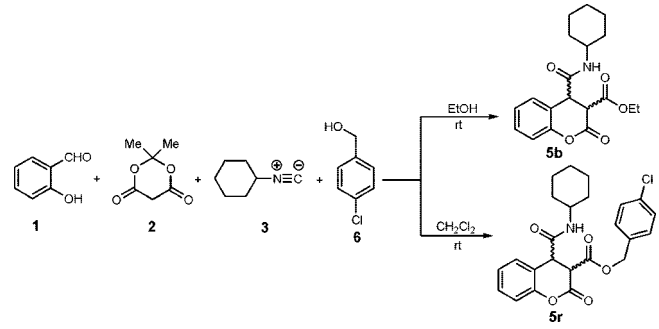
Table 2. Synthesis of 3,4-Dihydrocoumarins from 2-Hydroxybenzaldehydes, Meldrum's Acid, Isocyanides, and Alcohols in Dichloromethane



R^1	R^2	X	product	yield (%) (cis/trans)
cyclohexyl	isobutyl	H	**5q**	73 (77:23)
cyclohexyl	4-cholorobenzyl	H	**5r**	78 (63:37)
cyclohexyl	4-flurobenzyl	5-Br	**5s**	80 (74:36)
2,6-dimethyl phenyl	heptane	H	**5t**	78 (77:23)
2,6-dimethyl phenyl	cycloheptane	H	**5u**	76 (72:38)
2,6-dimethyl phenyl	cyclododecanol	H	**5x**	75 (100)

reaction mixture obtained from products (except **5e**, **5p**, and **5x**) was consistent with two diastereoisomers. On the basis

Scheme 2. Relation Reaction in EtOH and CH_2Cl_2



of single-crystal X-ray analysis and ROESY NMR data, the cis diastereoisomer is the major isomer. It is noteworthy that by increasing the size of alcohol or isocyanide, the diastereoselectivity of reaction was increased. For example in the case of cyclododecanol as alcohol (**5x**), or 4-tolune-methylsulfonylisocyanide as isocyanide (**5e** and **5p**) only the cis diastereoisomer is produced.

As can be seen in Tables 1 and 2, the reactions were carried out faster in MeOH or EtOH (5−8 h) than in CH_2Cl_2 (24−36 h).

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. Three substitutions in the products can be varied independently of each other. Owing to the great diversity of substitution

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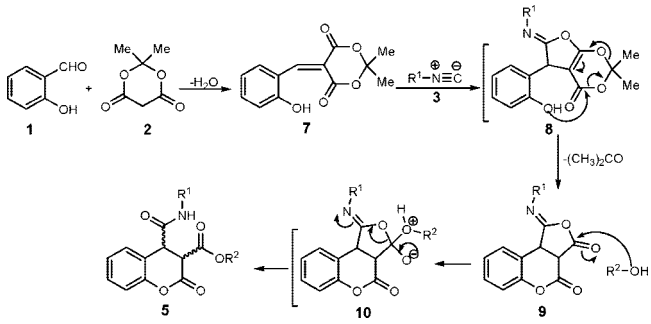
Scheme 3. Proposed Mechanism



patterns, this reaction may be used in the production of combinatorial libraries. Representative examples of this reaction are shown in Tables 1 and 2.

Mechanistically, the reaction may be rationalized as by initial formation of conjugated electron-deficient heterodiene by standard Knoevenogel condensation of the 2-hydroxybenzaldehydes **1** and Meldrum's acid **2**,[19] followed by a [4 + 1] cycloaddition reaction[20] or a Michael-type[21] addition reaction with isocyanide **3** to afford an iminolactone intermediate **8**. It is well known that acylated Meldrum's acid is readily transformed into β-ketoesters by alcoholysis,[22] so it is reasonable to assume that the intramolecular reaction of iminolactone with hydroxy group of 2-hydroxybenzaldehyde and subsequently loss of acetone from **8** leads to formation of **9**. Then, nucleophilic attack of alcohol to the activated carbonyl moiety of **9**, yields product **5** (Scheme 3).

In conclusion, we reported a novel four-component reaction leading to highly functionalized 3,4-dihydrocoumarin derivatives starting from simple and readily available inputs under neutral conditions without any activation or modifications. The reaction has been shown good functional group tolerance and is high yielding and product isolation is very straightforward. We hope that this approach may be of value to others seeking novel synthetic fragments with unique properties for medicinal chemistry programs.

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Supporting Information Available: Experimental procedures and characterization data of products, IR, mass, ^{1}H and ^{13}C NMR, and crystallographic data for **5a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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