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One-pot synthesis of 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives via a four-component reaction

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Abstract

An effective route to functionalized 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives is described. This involves reaction of *N*-alkyl-3-oxobutanamides, which result from the addition of an amine to the diketene, and a primary amine in the presence of dibenzoylacetylene. The 1,3-dicarbonyl compounds obtained from the addition of an amine to diketene were trapped with a primary amine to produce (*Z*)-3-(alkylamino)-N^1-alkyl-2-butenamide, which reacts with dibenzoylacetylene to produce 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives.

Keywords: Dibenzoylacetylene; Diketene; Primary amine; 4,5-Dihydro-1*H*-pyrrol-3-carboxamide; Multicomponent reaction

1. Introduction

The syntheses of pyrroles are by all means an attractive area in heterocyclic chemistry,[1] due primarily to the fact that many pyrroles are subunits of natural products[2] and some are the building blocks for porphyrin synthesis.[3] In particular, 3,4-disubstituted 1*H*-pyrroles have generated considerable interest owing to their remarkable diversity of biological activity.[4] A number of these compounds have been shown to possess antidiabetic,[5a] fungicidal,[5b] or antibacterial[5c] properties.

Pyrrole derivatives, especially the methyl homologs, are found in coal tar and bone oil. The biological importance of pyrrole and its derivatives cannot be overemphasized, because several natural pigments, such as heme, chlorophyll, bile pigments, or enzymes like the various cytochromes, include the pyrrole nucleus. Many alkaloids and at least two amino acids, namely, proline and hydroxyproline, also contain the reduced pyrrole ring (pyrrolidine).

However, it is also noteworthy that the 3,4-disubstituted pyrrole system is probably the most difficult to be prepared since most electrophilic aromatic substitution reactions as well as lithiation reactions of pyrrole rings occur predominantly at the α-position.[6] Selective substitutions at one or more of the β-positions have been generally believed to be a challenging goal in many synthetic programs. In the literature, several approaches to 3,4-disubstituted pyrroles have been recorded,[7] but it appears that they are less versatile for the realization of more elaborate substitution patterns.

In the context of our ongoing studies on heterocyclic construction mediated by enaminone intermediates,[8,9] the possibility of trapping the intermediate formed between two same or different amines and diketene with dibenzoylacetylene appeared attractive from the viewpoint of devising a novel MCR.

We wish to report a simple one-pot four-component reaction between two amines and diketene in the presence of dibenzoylacetylene leading to 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives **3** (Scheme 1).

2. Results and discussion

The reaction proceeded via a smooth 1:1:1:1 addition in dichloromethane at ambient temperature, to produce 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives **3** in 85–95% yields (Scheme 1).

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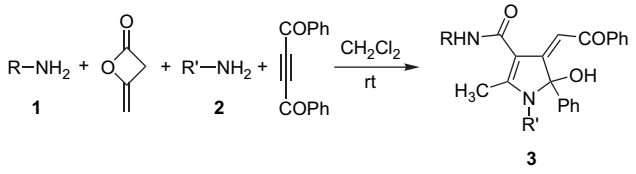


3	R	R'	%Yield of 3
a	*n*-pr	*i*-Bu	95
b	*i*-Bu	*n*-pr	90
c	*i*-pr	*i*-Bu	95
d	*i*-Bu	*i*-pr	90
e	*i*-Bu	*i*-Bu	90
f	*n*-pr	*n*-pr	85
g	*t*-Bu	*i*-Bu	90
h	*t*-Bu	*n*-pr	90

Scheme 1.

The structure of compounds **3a–h** was deduced from their elemental analysis, IR, high-field ^{1}H, and ^{13}C NMR spectra. Compound **3b** was further elucidated by a single crystal X-ray diffraction analysis. The molecular structure of **3b** is shown in Figure 1.

Although the mechanism of the reaction between dibenzoylacetylene and (*Z*)-3-(alkylamino)-*N*^{1}-alkyl-2-butenamide **5**, which was derived from the reaction of two amines with diketene, has not yet been established in an experimental manner, a possible explanation is proposed in Scheme 2. It is reasonable to assume that **3** results from initial addition of an amine to diketene,[10] which leads to *N*-alkyl-3-oxobutanamide **4** and subsequent reaction of the 1:1 adduct by the another primary amine produces (*Z*)-3-(alkylamino)-*N*^{1}-alkyl-2-butenamide **5**. Then, dibenzoylacetylene might be attacked by the (*Z*)-3-(alkylamino)-*N*^{1}-alkyl-2-butenamide **5** to form intermediate

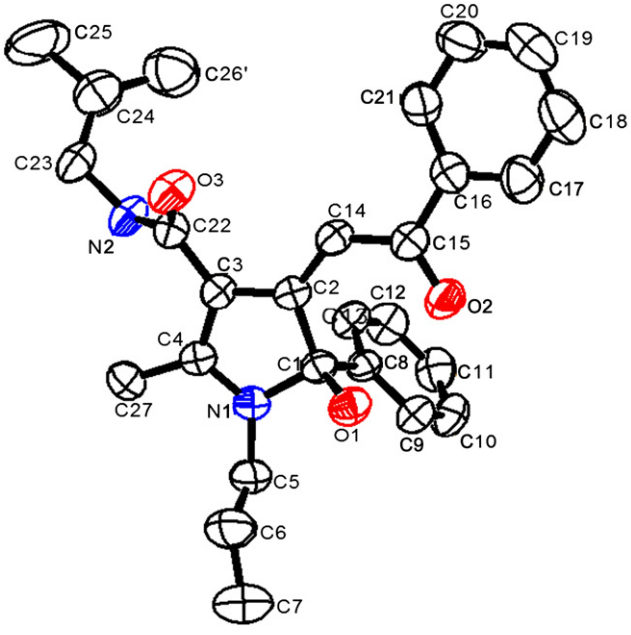
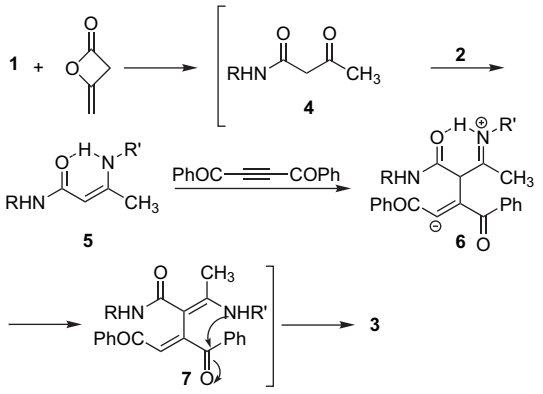


Figure 1.



Scheme 2.

6, which in turn is converted to intermediate **7**. Cyclization of the intermediate **7** leads to compound **3** (see Scheme 2).

3. Conclusion

In summary, the reaction between two primary amines and diketene in the presence of dibenzoylacetylene provides a simple one-pot entry into the synthesis of 4,5-dihydro-1*H*-pyrrol-3-carboxamide derivatives of potential synthetic and pharmaceutical interest. The present method carries the advantage of being performed under the neutral conditions and requiring no activation or modification of the educts. The simplicity of the present procedure makes it an interesting alternative to complex multistep approaches.[11]

4. Experimental

4.1. General

Melting points were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. IR spectra were recorded on a Shimadzu IR-460 spectrometer. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. ^{1}H and ^{13}C NMR spectra were recorded at 500.1 and 125.7 MHz, respectively, on a BRUKER DRX 500-AVANCE FT-NMR instrument with $CDCl_3$ as solvent. The reagents and solvents used in this work were obtained from Fluka (Buchs, Switzerland) and used without further purification. Dibenzoylacetylene was prepared according to a published procedure.[12,13]

4.2. General procedure for the preparation of compounds *3a–h*, exemplified on *3a*

To a magnetically stirred solution of *n*-propylamine (0.059 g, 1 mmol) and diketene (0.084 g, 1 mmol) in 5 mL dry CH_2Cl_2 for 2 h was added isobutylamine (0.073 g, 1 mmol), finally after 2 h was added dropwise a solution of dibenzoylacetylene (0.23 g, 1 mmol) in 3 mL dry CH_2Cl_2 at room temperature over 10 min. The reaction mixture was allowed to stir for 2 h.