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An unexpected and novel synthesis of pyrrole derivatives via isocyanide-based multicomponent reactions

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Abstract: The 1:1 intermediate, generated by the addition of cyclohexyl isocyanide to dialkyl acetylenedicarboxylates was trapped by cyclohexyl isocyanate in a one-pot three-component reaction to give alkyl 1-cyclohexyl-4-(cyclohexylcarbamoyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate derivatives in good yields without using any catalyst and activation.

Keywords: Cyclohexyl Isocyanide, Pyrrole derivatives, Three-component reactions, Cyclohexyl isocyanate**.**

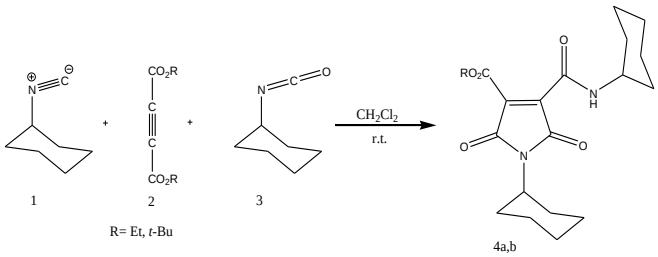
Introduction

Heterocyclics are of immense importance not only biologically and industrially but also to the functioning of any developed human society as well, the majority of pharmaceutical products that mimic natural products with biological activity are heterocycles [1]. As an important kind of these heterocycles, nitrogen-containing heterocycles as recognized pharmacophores have received great attention in drug discovery and lead optimization [2,3].

In recent years MCRs are a powerful tool for heterocycles synthesis. Due to the unique reactivity of the isocyanide-based MCRs (I-MCRs) are among the most versatile, in terms of the number and variety of compounds that can be generated [4-7].

A recently developed class of IMCRs is the reaction of isocyanides with electron-deficient acetylenes in the presence of an electrophile. A wide variety of electrophiles has been applied to trapped isocyanide-dialkyl acetylenedicarboxylate intermediate; among them are carbon electrophiles such as aldehyde [8,9], quinones[8], imines[10], and isocyanates [11].

As a part of our current studies on the development of new routes in heterocyclic synthesis[12-15], we report the results of our studies involving the reaction of the zwitterionic intermediate derived from cyclohexyl isocyanide **1** and acetylenic ester **2** with cyclohexyl isocyanate **3**, which constitutes a synthesis of highly functionalized alkyl 1-cyclohexyl-4-(cyclohexylcarbamoyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate derivatives **4** in good yields (Scheme **1**).



4	R	Yield%
a	Et	82
b	*t*-Bu	85

Scheme 1: Synthesis of alkyl 1-cyclohexyl-4-(cyclohexylcarbamoyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate derivatives.

Results and discussion

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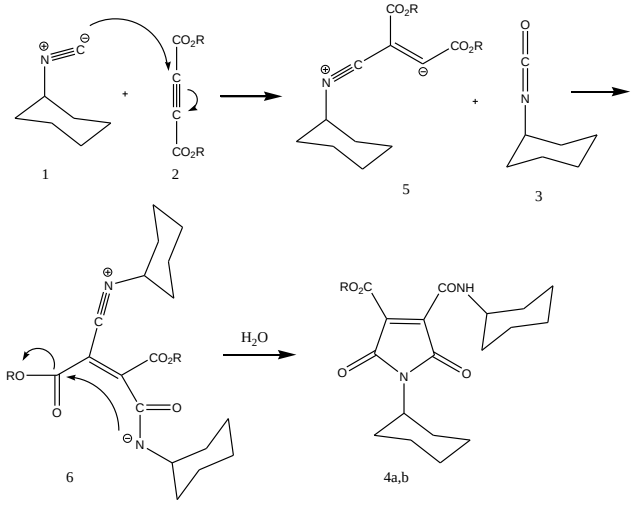
We have recently reported the reaction between alkyl/aryl isocyanides and dialkyl acetylenedicarboxylates in the presence of phenyl isocyanate[16]. This one-pot, three component synthesis has proceeded spontaneously at 38 ºC in CH_2Cl_2 and led to afford dialkyl 2-(alkyl/arylimino)-2,5-dihydro-5-oxo-1-phenyl-1*H*-pyrrole derivatives.

In this context, and in view of our interest in the multicomponent reaction[17-20], we now report the results of our study involving the reaction of cyclohexyl isocyanate **3** with cyclohexyl isocyanide **1** and acetylenic ester **2**, in dichloromethane at room temperature, which constitue a novel synthesis of pyrrole derivatives. The structure of compounds **4a, b** have been determined by IR, ^{1}H NMR, ^{13}C NMR, mass spectrometry and CHN elemental analysis. The ^{1}H NMR spectrum of compound **4b** exhibited a multiplet for ten CH_2 of two cyclohexyl rings (δ 1.08-1.97 ppm), a sharp singlet for the tert-butyl group at δ = 1.58 ppm because of the elimination of one tert-butoxy group, two multiplets for the two N-CH cyclohexyl proton (δ 3.51 and 3.77 ppm), and one doublet for NH at δ = 4.12 ppm with J = 7.6 Hz. The ^{13}C NMR spectra of two compounds displayed resonances in agreement with proposed structure and confirmed alkoxy group elimination. The IR spectrum of compound **4b** showed strong absorption at 3325 cm^{-1} relevant to the NH group and absorption at 1738 cm^{-1} attributed to ester carbonyl. The mass spectra of compounds **4a, b** displayed M^+ peak at appropriate *m/z* values.

The proposed mechanism may be explained the products formation (Scheme **2**). On the basis of the well established chemistry of isocyanides[20,21], it is reasonable to assume that compounds **4a, b** result from initial addition of cyclohexyl isocyanides **1** to the dialkyl acetylenedicarboxylates **2** and concomitant addition to cyclohexyl isocyanate **3** leading to intermediate **6**, then elemintion of alkoxy group and hydrolyzing the isocyanide group with water led to synthesis of pyrrole ring **4a, b**.



Scheme 2: Proposed mechanism for the formation of compound **4a, b**.

Conclusion

In conclusion, we observed a different treatment from cyclohexyl isocyanate in the reaction with cyclohexyl isocyanide and acetylenic esters that led to afford alkyl 1-cyclohexyl-4-(cyclohexylcarbamoyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate derivatives in good yields. Recent reactions show that how changes in temperature and branch chain of isocyanate could be effect on stability of the intermediate for generation of new compounds. The present procedure has the advantage that not only is the reaction performed under neutral conditions but also the reactants can be mixed without any activation or modification.

Experimental

Cyclohexyl isocyanate, cyclohexyl isocyanideand, dialkyl acetylenedicarboxylates were purchased from Fluka, Merk and Aldrich and used without further purification. Melting points, and IR spectra were measured on an Electrothermal 9100 apparatus, and a Shimadzu IR–460 spectrometer, respectively. The ^{1}H and ^{13}C NMR spectra were recorded on a BRUKER DRX–400 AVANCE instrument with $CDCl_3$ as solvent at 400.1 and 100.6 MHz, respectively. Mass spectra were recorded on a Shimadzu GC/MS QP 1100 EX mass spectrometer operating at an ionization potential

of 70 eV. Elemental analyses for C, H and N were recorded on a Heraeus CHN–O-Rapid analyzer.

General procedure:

The process for the preparation pyrrole derivatives is described for **4b** as an example. The solution of cyclohexyl isocyanide (1 mmol) in 3 mL of CH_2Cl_2 solvent was slowly added dropwise to a mixture of cyclohexyl isocyanate (1mmol) and di-tert-butyl acetylenedicarboxylate (1 mmol) in 20 mL of CH_2Cl_2 solvent at room temperature for 3 min. After the addition, the solution was stirring for 24 h. Then, the solvent was removed under reduced pressure, the solid product washed with mixture of cold diethyl ether and n-hexane with 1: 3 ratio (2×3 mL). The liquid phase was filtered off and residual recrystallized from diethyl ether.

Ethyl 1-cyclohexyl-4-(cyclohexylcarbamoyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(4a):***

Pale yellow powder, yield 82%, 0.34 g, mp 69-71 ºC; IR (KBr) (ν_{max}, cm^{-1}): 3329 (NH), 1738 (C=O of ester). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.08-1.88 (20H, m, $10CH_2$), 1.32 (3H, t, ^3J = 7.2 Hz, CH_3), 3.41 (1H, m, N-CH), 3.74 (1H, m, N-CH), 4.21 (1H, d, *J* = 7.5 Hz, NH), 4.34 (2H, q, ^3J = 7.2 Hz, OCH_2). ^{13}C NMR (100.1 MHz, $CDCl_3$): δ_C 13.9 (CH_3), 24.5, 25.0, 25.6, 25.8, 27.9, 28.3, 28.5, 29.1, 33.3 and 34.0 ($10CH_2$ of cyclohexyl), 49.2 (OCH_2), 57.9 and 62.3 (2N-CH), 136.2 and 148.9 ($C=C_{pyrrole\ ring}$), 156.7, 160.1, 166.6 and 168.3 (4CO). MS, *m/e* (%) = 376 (M^+, 5), 331 (5), 293 (6), 143 (57), 99 (62), 56 (100); Anal. Calcd for $C_{20}H_{28}N_2O_5$ (376.45): C, 63.81; H, 7.50; N, 7.44%. Found: C, 63.99; H, 7.59; N, 7.51%.

Tert-butyl 1-cyclohexyl-4-(cyclohexylcarbamoyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate ***(4b)****:*

Pale yellow powder, yield 85%, 0.34 g, mp 55-57 ºC; IR (KBr) (ν_{max}, cm^{-1}): 3325 (NH), 1738 (C=O of ester). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.58 (9H, s, $C(CH_3)_3$), 1.08-1.97 (20H, m, $10CH_2$), 3.51 (1H, m, N-CH), 3.77 (1H, m, N-CH), 4.12 (1H, d, *J* = 7.6 Hz, NH). ^{13}C NMR (100.1 MHz, $CDCl_3$): δ_C 24.3, 24.9, 25.6, 25.7, 27.9, 28.1, 28.5, 28.9, 33.4 and 33.9 ($10CH_2$ of cyclohexyl), 28.2 ($2C(CH_3)_3$), 49.1 and 57.2 (2N-CH), 83.9 ($OCMe_3$), 136.1 and 148.4 ($C=C_{pyrrole\ ring}$), 156.7, 159.5, 166.0 and 167.2 (4CO). MS, *m/e* (%) = 404 (M^+, 12), 330 (50), 303 (31), 98 (33), 83 (51), 57 (100); Anal. Calcd for $C_{22}H_{32}N_2O_5$ (404.50): C, 65.32; H, 7.97; N, 6.93%. Found: C, 65.68; H, 8.12; N, 7.03%.

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