Iranian Journal of Organic Chemistry Vol. 6, No. 4 (2014) 1369-1372

An efficient one-pot synthesis of *tert*-butyl 4-(alkylcarbamoyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate

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Received: September 2014; Revised: September 2014; Accepted: October 2014

Abstract: A convenient and efficient synthesis is described for the preparation of *tert*-butyl 4-(alkylcarbamoyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate via one-pot three-component reaction between *tert*-butyl isocyanide, dialkyl acetylenedicarboxylate and 2,6-dimethylphenyl isocyanate in dichloromethane without using any catalyst at room temperature in good yields.

Keywords: Pyrrole derivatives, Three-component reaction, Isocyanate, Acetylenic esters, One-pot.

Introduction

Pyrrole derivatives are considerable attention of synthetic importance and extensively used in drug discovery[1] and pharmacological activity such as anti-inflammatory [2], cytotoxicity [3, 4], *in vitro* cytotoxic activity against solid tumour models [5, 6], treatment of hyperlipidemias [7], antitumour agents [8]. The pyrrole containing heterocyclic derivatives have been reported in synthetic and effective biological importance [9, 10]. Pyrrole derivatives have biological activity such as COX-1/COX-2 inhibitors [11] and cytotoxic activity against a variety of marine and human tumor models [12]. We are interested in the synthesis of heterocyclic compounds. Thus, for this study, we are report novel pyrrole derivatives via one-pot three-component reaction.

Multi-component processes are at a premium for the achievement of high levels of diversity and brevity, as they allow three or more simple and flexible building blocks to be combined in practical, one-pot operations [13-15]. MCRs that involve isocyanides are by far the most versatile reactions in terms of scaffolds and number of accessible compounds. A number of advantages make MCRs very popular in the community of combinatorial chemists: superior atom economy, simple procedures, the one-pot character, and the high and ever-increasing number of accessible backbones.

In continuation of our interest in the application of isocyanides in heterocyclic compounds synthesis [16-21] we now report the reaction between *tert*-butyl isocyanide **3**, dialkyl acetylenedicarboxylate **2** and 2,6-dimethylphenyl isocyanate **1** in good yields (Scheme **1**).

Results and discussion

We have recently reported the synthesis of dialkyl 2-(alkyl/arylimino)-2,5-dihydro-5-oxo -1-phenyl-1*H*-pyrrole and alkyl 1-cyclohexyl-4-(cyclohexyl carbamoyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate derivatives [22, 23]. Considering the

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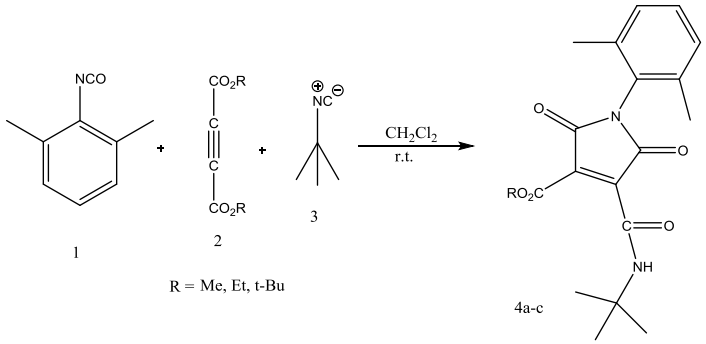
synthetic utility of heterocyclic compounds, now we describe a new multicomponent reaction for the synthesis of pyrrole derivatives **4**. As a part of our current studies on the development of new reactions of organic compounds, we report a convenient and facile synthesis of highly functionalized pyrrole derivatives **4a-c** in dichloromethane at room temperature in good yields.

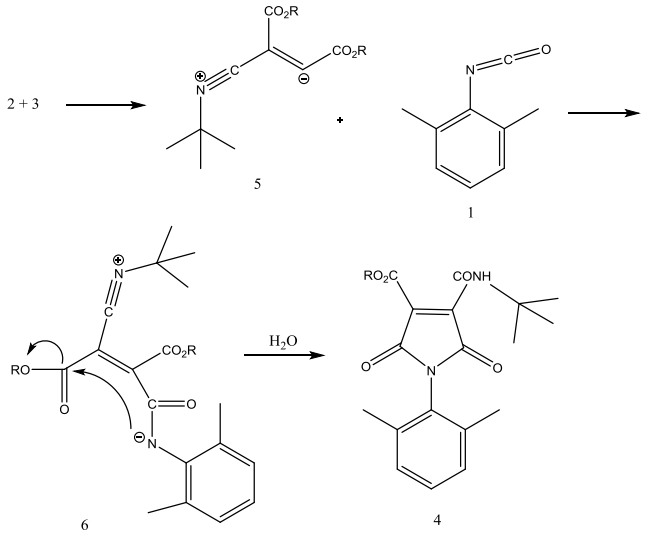


4	R	Yield%
4a	Me	90
4b	Et	83
4c	t-Bu	86

Scheme 1: Synthesis of *tert*-butyl 4-(alkylcarbamoyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate derivatives.

To obtain *tert*-butyl 4-(alkylcarbamoyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate derivatives, first *tert*-butyl isocyanide **3** was reacted with the acetylenic ester **2** to form intermediate **5** (Scheme **2**). The 1:1 zwitterionic intermediate **5** which adds to the isocyanate **1** leading to a dipolar species **6**, then elemintion of alkoxy group and hydrolyzing the isocyanide group with water led to synthesis of pyrrole derivatives **4a-c**. The cyclization and subsequent hydrolysis were conducted in one pot.

Products **(4a-c)** are stable solids which structures deduced from their IR, ^{1}H NMR, ^{13}CNMR, Mass spectral data and elemental analysis. The ^{1}H NMR spectrum of compound **4a** exhibited a sharp singlet for *tert*-butyl group at δ = 1.25 ppm, a sharp singlet for the two methyl groups at δ = 2.09 ppm, a singlet for the methoxy group at δ = 3.95 ppm and NH proton resonated at δ = 6.91 ppm supporting the IR absorption at 3278 cm^{-1}. The aromatic hydrogens gave rise to characteristic multiplet signal in the aromatic region of the spectrum δ = 6.94-7.25 ppm.



Scheme 2: The plausible mechanism for the synthesis of pyrrole derivatives.

Conclusion

In conclusion, we have found that the reaction of *tert*-butyl isocyanide with dialkyl acetylenedicarboxylates in the presence of 2,6-dimethylphenyl isocyanate leads to the one-pot three-component synthesis of highly functionalized *tert*-butyl 4-(alkylcarbamoyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-2,5-dihydro-1*H*-pyrrole-3-carboxylate. The presented reactions provide a simple entry into the synthesis of functionalized pyrroles derivatives of potential synthetic and pharmaceutical interest. This work has number of advantages including: neutral conditions, good yield, not use of any activation or modification.

Experimental

2,6-Dimethylphenyl isocyanate, *tert*-butyl isocyanide, and dialkyl acetylenedicarboxylate 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 JASCO FT-IR spectrometer, respectively. The ^{1}H NMR 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 were performed using a Heraeus CHN-O-Rapid analyser.

General procedure:

The process for the preparation pyrrole derivatives is described for **4a** as an example. The solution of *tert*-butyl isocyanide (1 mmol) in 3 mL of CH_2Cl_2 solvent was slowly added dropwise to a mixture of 2,6-dimethylphenyl isocyanate (1mmol) and dimethyl 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 to afford the pure product.

Methyl 4-(tert-butylcarbamoyl)-1-(2,6-dimethylphenyl) -2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**4a**):

Orange powder (0.32 g, 90%); m.p. 85-87 ˚C; IR (KBr) (ν_{max}, cm^{-1}): 3278 (NH), 1736 (C=O of ester).; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.25 (9H, s, $C(CH_3)_3$), 2.09 (6H, s, $2CH_3$), 3.95 (3H, s, OCH_3), 6.91 (1H, br, NH), 6.94-7.25 (3H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 18.5 ($2CH_3$), 28.4 ($C(CH_3)_3$), 52.2 (N-CMe_3), 63.0 (OCH_3), 127.7, 127.8, 128.3, 130.5(C_{arom}), 135.3 and 142.6 ($C=C_{pyrrole\ ring}$), 155.6, 159.8, 164.0 and 166.0 (4CO).; MS, *m/e* (%) = 358 (M^+, 20), 357(77), 341 (50), 301 (14), 225 (100), 198 (35), 57 (60); Anal. Calcd for $C_{19}H_{22}N_2O_5$ (358.39): C, 63.68; H, 6.19; N, 7.82; Found: C, 63.76; H, 6.22; N, 7.85%.

Ethyl 4-(tert-butylcarbamoyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**4b**):

Pale orange powder (0.31 g, 83%); m.p. 89-91˚C; IR (KBr) (ν_{max}, cm^{-1}): 3269 (NH), 1739 (C=O of ester).; ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.31 (H, t, $^3J_{HH}$ = 7.0 Hz, CH_3),1.38 (9H, s, $C(CH_3)_3$), 2.14 (6H, s, $2CH_3$), 4.35 (q, $^3J_{HH}$ = 7.0 Hz, OCH_2), 6.86 (1H, br, NH), 7.11-7.30 (3H, m, Ar-H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ_C 14.1 (CH_3), 18.7 ($2CH_3$), 29.2 ($C(CH_3)_3$), 54.0 (N-CMe_3), 62.7 (OCH_2), 127.5, 128.3, 129.0, 129.8 (C_{arom}), 134.6 and 136.6 ($C=C_{pyrrole\ ring}$), 158.1, 159.4, 162.4 and 167.5 (4CO).; MS, *m/e* (%) = 372 (M^+, 12), 371 (15), 327 (65), 315 (50), 301 (14), 298 (100), 105 (35), 73 (21), 57 (44); Anal. Calcd for $C_{20}H_{24}N_2O_5$ (372.42): C, 64.50; H, 6.50; N, 7.52; Found: C, 64.59; H, 6.52; N, 7.57%.

Tert-butyl 4-(tert-butylcarbamoyl)-1-(2,6-dimethylphenyl)-2,5-dioxo-2,5-dihydro-1H-pyrrole-3-carboxylate (**4c**):

Orange powder, (0.34 g, 86%); m.p. 95-97 ºC; IR (KBr) (ν_{max}, cm^{-1}): 3351 (NH), 1735 (C=O of ester). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ_H 1.34 (9H, s, N-$C(CH_3)_3$), 1.65 (9H, s, $OC(CH_3)_3$), 2.21 (6H, s, $2CH_3$), 6.93 (1H, br, NH), 6.99-7.31 (3H, m, Ar-H);. ^{13}C NMR (100.1 MHz, $CDCl_3$): 18.3 ($2CH_3$), 27.8 ($NC(CH_3)_3$), 29.4 ($OC(CH_3)_3$), 56.9 (N-CMe_3), 82.4 ($OCMe_3$), 127.5, 127.7, 128.8, 131.2 (C_{arom}), 136.5 and 139.6 ($C=C_{pyrrole\ ring}$), 157.0, 158.6, 165.9 and 168.0 (4CO). MS, *m/e* (%) = 400 (M^+, 36), 343 (48), 299 (30), 194 (56), 105 (63), 77 (18), 57 (100); Anal. Calcd for $C_{22}H_{28}N_2O_5$ (400.47): C, 65.98; H, 7.05; N, 7.00; Found: C, 66.05; H, 7.05; N, 7.07%.

Acknowledgement

We gratefully acknowledge financial support from the Research Council of University of Sistan and

Baluchestan and Islamic Azad University, Zahedan Branch.

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