Recyclization of methyl 1-aryl-3-cinnamoyl-4,5-dioxo-4,5-dihydro-1H-pyrrole-2-carboxylates in reaction with monosubstituted hydrazines

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DOI: <http://dx.doi.org/10.3998/ark.5550190.p009.068>

Abstract

Methyl 1-aryl-3-cinnamoyl-4,5-dioxo-4,5-dihydro-1H-pyrrole-2-carboxylates react with phenylhydrazine or benzylhydrazine to give the corresponding methyl 1-(phenyl or benzyl)-5-(arylcabamoyl)-4-cinnamoyl-1H-pyrazole-3-carboxylates in good yields. The structures of the compounds obtained were proved by 1D ¹H, ¹³C and 2D NMR experiments.

Keywords: Pyrrole-2,3-diones, hydrazines, recyclization, pyrazoles, 2D NMR

Introduction

As an important class of heteroaromatic ring systems, pyrazoles have found widespread application in the agrochemical, material, and especially pharmaceutical industries.¹⁻⁴ The syntheses of pyrazoles have drawn considerable attention from organic chemists because of their diverse bioactivities.⁵⁻⁸ Recyclization of 1H-pyrrole-2,3-diones by the action of monosubstituted hydrazines is a convenient method of synthesis of polyfunctional pyrazoles. These recyclization proceeds with the carbonyl group of acyl substituent at the C⁴ of heterocycle^{9,10} or ketone carbonyl group of dioxopyrrole.¹¹ Reactions of methyl 1-aryl-3-cinnamoyl-4,5-dioxo-4,5-dihydro-1H-pyrrole-2-carboxylates with hydrazine derivatives were not studied.

Results and Discussion

Methyl 1-aryl-3-cinnamoyl-4,5-dioxo-4,5-dihydro-1*H*-pyrrole-2-carboxylates **1a-c** react with an equimolar amount of phenylhydrazine **2a** or benzylhydrazine **2b** under reflux for 20-30 min in anhydrous 1,4-dioxane (TLC control) to afford methyl 1-(phenyl or benzyl)-5-(arylcarmoyl)-4-cinnamoyl-1*H*-pyrazole-3-carboxylates **3a-f** in good yield (Scheme 1).

1, Ar = Ph (a), C₆H₄Me-4 (b), C₆H₄OMe-4 (c); **2**, R = Ph (a), CH₂Ph (b); **3**, Ar = Ph, R = Ph (a), CH₂Ph (b); Ar = C₆H₄Me-4, R = Ph (c), CH₂Ph (d); Ar = C₆H₄OMe-4, R = Ph (e), CH₂Ph (f)

Scheme 1. Recyclization of pyrrolediones **1a-c** in the reaction with monosubstituted hydrazines.

Compounds **3a-f** are the colorless or light yellow crystals readily soluble in dimethylsulfoxide (DMSO) and dimethylformamide (DMF), hardly soluble in alcohols, ethers, chlorinated solvents, aromatics and insoluble in saturated hydrocarbons and water.

The molecular structures of compounds **3a-f** were confirmed with by spectral and analytical data. For example, the IR spectra of **3a-f** contain stretching bands of the amide NH-group as broadened bands in a range of 3253-3315 cm⁻¹, the stretching bands of the ester carbonyl group at 1717-1733 cm⁻¹, the stretching bands of the amide carbonyl group at 1667-1685 cm⁻¹, the stretching bands of the ketone carbonyl group at 1635-1655 cm⁻¹, the stretching bands of the cinnamoyl HC=CH group at 1615-1625 cm⁻¹, and amide II band was observed at 1553-1566 cm⁻¹.

Analysis of the ¹H NMR spectra (DMSO-d₆) of compounds **3a-f** has show that besides the signals inherent to the protons of aromatic rings and the substituents attached thereto, the spectra exhibited a singlet from the methoxycarbonyl protons at δ 3.80–3.86 ppm, doublets from protons at the double bond in the cinnamoyl fragment at δ 7.24–7.61 ppm with a coupling constant ³*J* of 15.8–16.1 Hz typical of trans-configured alkenes¹² and a signal from the amide NH proton at δ 10.72–10.95 ppm. Methylene protons in the benzyl substituent of compounds **3b,d,f** resonated as a singlet at δ 5.55–5.56 ppm.

In the ¹³C NMR spectra of compounds **3b,d,e** apart from signals typical of carbon atoms in the aromatic rings, substituents therein, methylene and methoxy groups, we observed signals from carbonyl carbon atoms at δ_C 185.7–185.9 (C⁴CO), 161.6–161.7 (COOMe), 156.7–157.1 (CONH) and signals from carbon atoms at the double bond in the cinnamoyl fragment at 143.4–144.4 (C⁴COCC), 126.3–126.5 (C⁴COC) ppm. The chemical shifts of carbons in the pyrazole ring were at

δ_{C} 140.7–141.8 (C^3), 140.1–140.3 (C^5), 122.8–123.3 (C^4) ppm. The chemical shifts of carbon in the benzyl substituent of compounds **3b,d** were at δ_{C} 54.6 ppm.

However, the ^1H and ^{13}C NMR spectral data did not allow performing an unambiguous choice between two possible structures (type A or B) of the recyclization products **3a-f** (Figure 1). In the absence of suitable crystals for X-ray analysis, we undertook a thorough analysis of the structures of pyrazoles **3** via NMR spectroscopy, including 2D ^1H - ^{13}C HSQC / HMBC and ^1H - ^1H NOESY experiments of compounds **3d,e** as an example (Figure 2). This made it possible to decide between two structures of pyrazoles **3** in favor of type B.

Figure 1. Types of pyrazoles **3a-f**.

The most downfield-shifted ^{13}C resonance in the ^{13}C spectra corresponds to the carbonyl carbon of cinnamoyl moiety (δ_{C} 185.8 and 185.9 ppm, respectively), as evidenced by correlations of these carbons with protons at the double bond $\text{H}^{2'}$, $\text{H}^{3'}$ in the 2D ^1H - ^{13}C HMBC spectra.

In the 2D HMBC spectrum of compound **3d**, cross-peaks between protons of NCH_2 -group and carbons C_i , C_o and C^5 (δ_{C} 140.2 ppm) are observed. The chemical shift of the pyrazole carbon C^5 in compound **3e** has a similar value (δ_{C^5} 140.1 ppm). The presence of low-intensity cross-peak between protons $\text{H}^{2'}$ and carbons C^4 (δ_{C^4} 122.8 and 123.3 ppm, respectively) in the HMBC spectra is characteristic for both compounds **3d, e**.

Figure 2. Key ^1H - ^{13}C long-range and ^1H - ^1H NOE connectivities for compounds **3d,e**.

The proposed pyrazole structure of type B is also confirmed by the data of 2D ^1H - ^1H NOESY experiment, which suggests that substituents at N^1 and C^5 in pyrazole are spatially close. In particular, the NH-proton of arylcarbamoyl substituent at C^5 in compound **3d** gives the cross-peak

with methylene protons of the benzyl substituent at N¹; and in compound **3e**, with ortho-protons of phenyl substituent at N¹ (Figure 3).

Figure 3. Fragments of ¹H-¹H NOESY (500 MHz, DMSO-*d*₆) spectra of **3d** (left) and **3e** (right).

The formation of compounds **3a-f** occurs apparently due to the initial addition of the primary amino group in monosubstituted hydrazine at the C² atom of dioxopyrrole **1a-c** with formation of intermediate **4** which undergoes cleavage of the pyrrole ring at the N¹-C² bond. The subsequent intramolecular nucleophilic attack by the secondary amino group in the hydrazine fragment on the carbonyl carbon atom neighboring to the carbamoyl fragment and elimination of water molecule yields final pyrazole structure **3a-f** (Scheme 2).

Scheme 2. The mechanism of formation **3a-f**.

Conclusions

We have succeeded in developing a method for synthesis of new functionalized pyrazole derivatives of potential synthetic and pharmacological interest from the recyclization of 1*H*-pyrrole-2,3-diones with phenylhydrazine or benzylhydrazine. Our work presents a very simple reaction performed under neutral conditions and in the absence of any catalyst. From a structural viewpoint, the products are polycarbonyl compounds suitable for further modification. High yields and the simple reaction and purification procedures are the key advantages of this approach.

Experimental Section

General. Melting points were obtained on a standard melting point apparatus in open capillary tubes. IR spectra (mineral oil) were recorded on a Perkin Elmer Spectrum Two spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded at 500.1 and 125.6 MHz respectively on a Bruker AVANCE^{III} 500 spectrometer with DMSO-*d*₆ as solvent and TMS as internal standard. All signals in the ^1H and ^{13}C NMR spectra of compounds **3d,e** were assigned on the basis of 2D ^1H - ^{13}C HSQC and HMBC experiments. All reactions were monitored by TLC (silica gel, Silufol aluminum sheets, benzene-ethyl acetate 5:1). Elemental analyses for C, H and N were obtained using a LECO CHNS-932 analyzer.

Methyl 1-(phenyl or benzyl)-5-(arylcarbamoyl)-4-cinnamoyl-1*H*-pyrazole-3-carboxylates (3a-f). **General procedure.** A solution of 1 mmol of hydrazine **2** in 5 mL of anhydrous 1,4-dioxane was added to a solution of 1 mmol of compound **1** in 20 mL of anhydrous 1,4-dioxane. The mixture was heated for 30 min under reflux, evaporated and recrystallized from ethanol.

Methyl 4-cinnamoyl-1-phenyl-5-(phenylcarbamoyl)-1*H*-pyrazole-3-carboxylate (3a). Colorless crystals, yield 80%, mp 209-210 °C; IR (ν_{max} , cm^{-1}): 3281 (NH), 1728 (COOMe), 1684 (CONH), 1649 ($\text{C}^4\text{-CO}$), 1621 (CH=CH), 1558 (NH). ^1H NMR (500 MHz, DMSO-*d*₆): δ_{H} 3.86 (3H, s, H^7), 7.10 (1H, t, J 7.4 Hz, $\text{H}^{6''}$), 7.29 (2H, t, J 7.8 Hz, 2CH_{arom}), 7.32 (1H, d, J 16.1 Hz, $\text{H}^{2'}$), 7.38-7.70 (13H, m, $\text{H}^{3'}$, $12\text{CH}_{\text{arom}}$), 10.95 (1H, s, NH). Anal. Calcd for $\text{C}_{27}\text{H}_{21}\text{N}_3\text{O}_4$ (451.48): C, 71.83; H, 4.69; N, 9.31%. Found: C, 71.79; H, 4.60; N, 9.26%.

Methyl 1-benzyl-4-cinnamoyl-5-(phenylcarbamoyl)-1*H*-pyrazole-3-carboxylate (3b). Colorless crystals, yield 83%, mp 168-170 °C; IR (ν_{max} , cm^{-1}): 3253 (NH), 1733 (COOMe), 1675 (CONH), 1648 ($\text{C}^4\text{-CO}$), 1620 (CH=CH), 1562 (NH). ^1H NMR (500 MHz, DMSO-*d*₆): δ_{H} 3.80 (3H, s, H^7), 5.56 (2H, s, NCH_2), 7.13 (1H, t, J 7.4 Hz, $\text{H}^{6''}$), 7.26 (1H, d, J 16.0 Hz, $\text{H}^{2'}$), 7.29-7.44 (10H, m, $10\text{CH}_{\text{arom}}$), 7.53 (1H, d, J 16.0 Hz, $\text{H}^{3'}$), 7.55 (2H, d, J 7.8 Hz, 2CH_{arom}), 7.65 (2H, d, J 7.8 Hz, $\text{H}^{5'}$), 10.87 (1H, s, NH). ^{13}C NMR (126 MHz, DMSO-*d*₆): δ_{C} 52.3 (C^7), 54.6 (NCH_2), 120.1 ($\text{C}^{4''}$), 122.9 (C^4), 124.7 ($\text{C}^{6''}$), 126.5 ($\text{C}^{2'}$), 128.0 (C^o), 128.2 (C^p), 128.5 ($\text{C}^{5'}$), 128.7 (C^m), 128.8 ($\text{C}^{5''}$), 128.9 ($\text{C}^{6'}$), 130.7 ($\text{C}^{7'}$), 134.2 ($\text{C}^{4'}$), 135.4 ($\text{C}^{3''}$), 137.7 (C^i), 140.1 (C^5), 140.7 (C^3), 143.4 ($\text{C}^{3'}$).

157.1 (C^{1''}), 161.7 (C⁶), 185.7 (C^{1'}). Anal. Calcd for C₂₈H₂₃N₃O₄ (465.51): C, 72.25; H, 4.98; N, 9.03%. Found: C, 72.30; H, 4.93; N, 9.06%.

Methyl 4-cinnamoyl-1-phenyl-5-(p-tolylcarbamoyl)-1H-pyrazole-3-carboxylate (3c). Colorless crystals, yield 81%, mp 209-210 °C; IR (ν_{max}, cm⁻¹): 3315 (NH), 1722 (COOMe), 1669 (CONH), 1635 (C⁴-CO), 1615 (CH=CH), 1553 (NH). ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 2.23 (3H, s, H^{7''}), 3.86 (3H, s, H⁷), 7.09 (2H, d, *J* 8.6 Hz, H^{5''}), 7.30 (1H, d, *J* 16.1 Hz, H^{2'}), 7.32 (2H, d, *J* 8.6 Hz, H^{4''}), 7.39-7.70 (11H, m, H^{3'}, 10CH_{arom}), 10.86 (1H, s, NH). Anal. Calcd for C₂₈H₂₃N₃O₄ (465.51): C, 72.25; H, 4.98; N, 9.03%. Found: C, 72.21; H, 4.94; N, 9.00%.

Methyl 1-benzyl-4-cinnamoyl-5-(p-tolylcarbamoyl)-1H-pyrazole-3-carboxylate (3d). Light yellow crystals, yield 82%, mp 156-157 °C; IR (ν_{max}, cm⁻¹): 3267 (NH), 1717 (COOMe), 1685 (CONH), 1647 (C⁴-CO), 1625 (CH=CH), 1561 (NH). ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 2.25 (3H, s, H^{7''}), 3.80 (3H, s, H⁷), 5.55 (2H, s, NCH₂), 7.13 (2H, d, *J* 8.2 Hz, H^{5''}), 7.25 (1H, d, *J* 16.1 Hz, H^{2'}), 7.29-7.43 (10H, m, 10CH, Ar, Ph), 7.52 (1H, d, *J* 16.1 Hz, H^{3'}), 7.65 (2H, d, *J* 7.2 Hz, H^{5'}), 10.78 (1H, s, NH). ¹³C NMR (126 MHz, DMSO-*d*₆): δ_C 20.5 (C^{7''}), 52.3 (C⁷), 54.6 (NCH₂), 120.1 (C^{4''}), 122.8 (C⁴), 126.5 (C^{2'}), 128.0 (C^o), 128.2 (C^p), 128.5 (C^{5'}), 128.7 (C^m), 128.9 (C^{6'}), 129.2 (C^{5''}), 130.7 (C^{7'}), 133.8 (C^{6''}), 134.2 (C^{4'}), 135.2 (C^{3''}), 135.5 (Cⁱ), 140.1 (C⁵), 140.7 (C³), 143.4 (C^{3'}), 156.9 (C^{1''}), 161.7 (C⁶), 185.8 (C^{1'}). Anal. Calcd for C₂₉H₂₅N₃O₄ (479.54): C, 72.64; H, 5.26; N, 8.76%. Found: C, 72.67; H, 5.28; N, 8.79%.

Methyl 4-cinnamoyl-5-((4-methoxyphenyl)carbamoyl)-1-phenyl-1H-pyrazole-3-carboxylate (3e). Colorless crystals, yield 80%, mp 195-196 °C; IR (ν_{max}, cm⁻¹): 3307 (NH), 1722 (COOMe), 1667 (CONH), 1636 (C⁴-CO), 1616 (CH=CH), 1553 (NH). ¹H NMR (500.1 MHz, DMSO-*d*₆): δ_H 3.70 (3H, s, H^{7''}), 3.86 (3H, s, H⁷), 6.86 (2H, d, *J* 9.1 Hz, H^{5''}), 7.30 (1H, d, *J* 16.0 Hz, H^{2'}), 7.35 (2H, d, *J* 9.1 Hz, H^{4''}), 7.40-7.46 (3H, m, H^{7'}, H^{6'}), 7.51 (1H, tt, *J* 7.3, *J* 1.2 Hz, H^p), 7.57 (2H, dd, *J* 8.4, *J* 7.3 Hz, H^m), 7.60 (1H, d, *J* 16.0 Hz, H^{3'}), 7.65 (2H, dd, *J* 8.4, *J* 1.2 Hz, H^o), 7.69 (2H, dd, *J* 7.7, *J* 1.8 Hz, H^{5'}), 10.81 (1H, s, NH). ¹³C NMR (126 MHz, DMSO-*d*₆): δ_C 52.5 (C⁷), 55.2 (C^{7''}), 114.0 (C^{5''}), 121.4 (C^{4''}), 123.3 (C⁴), 123.8 (C^o), 126.3 (C^{2'}), 128.6 (C^{5'}), 129.0 (C^{6'}), 129.3 (C^p), 129.6 (C^m), 130.7 (C^{3''}), 130.8 (C^{7'}), 134.2 (C^{4'}), 138.2 (Cⁱ), 140.3 (C⁵), 141.8 (C³), 144.4 (C^{3'}), 156.2 (C^{6''}), 156.7 (C^{1''}), 161.6 (C⁶), 185.9 (C^{1'}). Anal. Calcd for C₂₈H₂₃N₃O₅ (481.51): C, 69.84; H, 4.81; N, 8.73%. Found: C, 69.89; H, 4.86; N, 8.74%.

Methyl 1-benzyl-4-cinnamoyl-5-((4-methoxyphenyl)carbamoyl)-1H-pyrazole-3-carboxylate (3f). Light yellow crystals, yield 82%, mp 178-179 °C; IR (ν_{max}, cm⁻¹): 3304 (NH), 1731 (COOMe), 1668 (CONH), 1655 (C⁴-CO), 1622 (CH=CH), 1566 (NH). ¹H NMR (500 MHz, DMSO-*d*₆): δ_H 3.72 (3H, s, H^{7''}), 3.80 (3H, s, H⁷), 5.55 (2H, s, NCH₂), 6.89 (2H, d, *J* 8.6 Hz, H^{5''}), 7.24 (1H, d, *J* 16.0 Hz, H^{2'}), 7.29-7.45 (10H, m, 10CH_{arom}), 7.52 (1H, d, *J* 16.0 Hz, H^{3'}), 7.65 (2H, m, H^{5'}), 10.72 (1H, s, NH). Anal. Calcd for C₂₉H₂₅N₃O₅ (495.53): C, 70.29; H, 5.09; N, 8.48%. Found: C, 70.23; H, 5.04; N, 8.46%.

Acknowledgements

The study was financially supported by the Ministry of Education and Science of the Russian Federation, by the Ministry of Education of Perm Krai (International Research Teams competition), and by the Russian Foundation for Basic Research (Grants Nos. 13-03-96009, 14-03-96014).

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