Scientific Research

A Facile Synthesis of 3-Styryltropono[*c*] Pyrazole Derivatives

Hong Zhang, Mingqin Chang, Wentao Gao*

Institute of Superfine Chemicals

Bohai University

Jinzhou City, Liaoning Province

Email: bhuzh@163.com

Abstract: A facile synthesis of some novel 3-styryltropono[*c*]pyrazole derivatives via the condensation reaction of 3-cinnamoyltropolones with phenylhydrazine is described. All the synthesized compounds were obtained in good yields of 67-88% and their structures were characterized by IR, ^{1}H NMR, MS, and elemental analysis.

Keywords: tropone, aldehydes, chalcone, claisen-schmidt condensation

1. Introduction

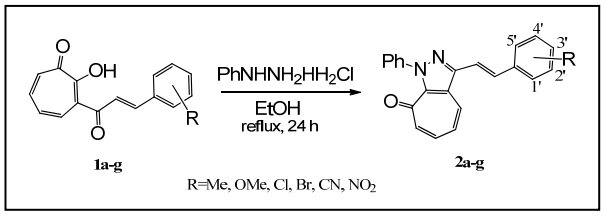
The pyrazole moiety is present in a wide variety of biologically active compounds[1-3]. Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative-hypnotic activity[4-7]. This class of compounds has also a rich chemistry because of their easy reductive cleavage and susceptibility to ring transformations. Thus, continuous efforts have been devoted to the development of more novel and interesting pyrazole derivatives[8-10]. Although the preparation of substituted pyrazoles has been extensively investigated, there has been an expansion of these studies to include fused-ring pyrazole derivatives[11-14].

On the other hand, troponoid natural products and synthetic troponoid derivatives have attracted considerable interest due to the unique structure and properties of the troponoid ring. Therefore, significant effort continues to be directed toward the development of new tropone structures[15-22]. Especially, there is much current interest in assembling tropone ring by fusing with heterocyclic systems, which represent privileged moieties in medicinal chemistry, and are ubiquitous sub-structures associated with biologically active natural products[23-26].

In light of these findings and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry for a faster and efficient lead generation towards the new drug discovery[27], the synthesis of novel pyrazoles fused to tropone ring would be much more attractive. Thus, we are very interested in transforming 3-cinnamoyltropolones into some novel 3-styryltropono[*c*]pyrazole derivatives

2. Results and discussion

In the context of our ongoing studies on troponoid chemistry and as a continuation of our previous work on the novel synthesis of some new troponoid compounds[28-34], we reported herein the synthesis of novel 3-styryltropono[*c*]pyrazole derivatives (**2a-g**) as shown in Scheme 1. The starting Compounds 1a-g were prepared according to the literature[33].



Scheme 1. Synthesis of the title compounds.

Initially, we examined the reaction of **1** with free phenylhydrazine in refluxing EtOH. However, the reaction was found to be very complex and we could not obtain any pyrazole derivatives in appreciable yields. Instead, we found that the reaction of **1** and phenylhydrazine hydrochloride was performed smoothly to give the desired (*E*)-3-(4-methylstyryl)-1-phenyltropono[*c*] pyrazole (**2a**) in good yield of 69%. The reaction result we obtained is very similar to the literature reported by Lee *et al*.[34] In addition, we also attempted to other solvents such as MeOH, MeCN, and 1,2-dichloroethane. But the yield could not be improved further. Some representative results are summarized in Table 1.

Table 1. Melting points and yields of compounds **3a-h**

Entry	Compd.	R	Mp/oC	Yield/%
1	**2a**	4'-Me	234-235	69
2	**2b**	2'-OMe	203-205	65
3	**2c**	4'-OMe	244-246	52
4	**2d**	4'-Cl	216-218	62

Table 1 (Continued)

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Entry	Compd.	R	Mp/oC	Yield/%
5	**2e**	2'-Br	209-211	50
6	**2f**	4'-CN	225-227	71
7	**2g**	4'-NO_2	238-240	51

As shown in Table **1**, the effect of substitution group on the benzene ring is not very strong, showing little distinction. For example, the troponyl-substituted chalcones **2a-c** (Entries 1-3) bearing electron-donating methyl and methoxy groups were obtained in 69%, 65% and 52% yields, respectively. On the other hand, compounds **2d-g** (Entries 4-7) bearing electron-withdrawing groups were obtained in the comparable yields of 50-71%.

The structures of all these newly synthesized **3**-styryltropono[*c*]pyrazole derivatives were established with the help of spectral data and elemental analysis. For example, the ir spectrum of reaction product **2a** showed a typical stretching vibration bands at 1636 cm^{-1} due to the tropone carbonyl. The main features of its ^1H NMR data are the resonances of the two vinylic protons appearing as two doublets at 7.47 and 7.66 ppm with a coupling constant *J*=16.0 Hz, which indicated the *E*-configuration of these vinylic systems. Its ESI-MS spectrum (positive-ion mode) exhibited a characteristic quasi-molecular ion peak at m/z 339.3 ($[M+H]^+$). Further, the structure assigned for this reaction product **2a** was fully supported by its elemental analysis, which established their molecular formulas in accordance with their suggested molecular structure.

It can be concluded that the present investigation has demonstrated a facile synthesis of novel 3-styryltropono[*c*]pyrazole derivatives. The molecules we have synthesized should allow us, in the future, to investigate structure-activity relationships over various biotests.

2. Experimental

The melting points were determined by using WRS-1B melting points apparatus and were uncorrected. ^1H NMR was measured with a BRUKER BRX 400 at 400 MHz. The reported chemical shifts were against TMS. Mass spectra (MS) were measured on a CU-TOF-MICRO spectrometer. Elemental analysis were recorded on an Elementar vario EL-Ⅲ element analyzer.

*General procedure for synthesis 3-styryltropono[c]pyrazole derivatives (**2a-g**)*

To a solution of 3-cinnamoyltropolone 1 (1 mmol) in 5 mL of EtOH was added phenylhydrazine hydrochloride (2 mmol). The resulting mixture was heated at reflux for 24 h. After the reaction was complete (TLC), the mixture was cooled to room temperature, and then poured into some water, filtered to give the crude products, which were further purified by recrystallization from acetic acid. The yields and melting points are listed in Table 1.

(*E*)-3-(4-methylstyryl)-1-phenyltropono[*c*]pyrazole (2a)

IR (KBr) ν : 1636, 1592, 1557, 1520, 1496, 1420, 1400, 1273, 1214, 1167, 1148, 1030, 1014, 960, 896, 852, 801, 700 cm-1; ^1H NMR ($CDCl_3$) δ : 2.33 (s, 3H, Me), 6.90 (d, 1H, *J*=12.4 Hz, tropone-H), 6.98-7.01 (m, 1H, ArH), 7.23 (d, 2H, *J*=8.0 Hz, benzene-H), 7.47 (d, 1H, *J*=16.0 Hz, =CH), 7.41-7.51 (m, 6H, ArH), 7.66 (d, 2H, *J*=8.0 Hz, benzene-H), 7.69 (d, 1H, *J*=16.4 Hz, =CH), 8.13 (d, 1H, *J*=10.8 Hz, tropone-H); MS (ES+): 339.3 $(M+H)^+$. Anal. Calcd for $C_{23}H_{18}N_2O$: C 81.63, H 5.36, N 8.28; Found: C81.24, H 5.47, N 8.35.

(*E*)-3-(2-methoxystyryl)-1-phenylcyclohepta[c] pyrazol-8(1H)-one (2b)

IR (KBr) ν : 1610, 1558, 1519, 1510, 1476, 1410, 1255, 1217, 1025, 974, 761, 702 cm-1; ^1H NMR (CDCl3) δ : 3.86 (s, 3H, OMe), 6.91 (d, 1H, *J*=12.4 Hz, tropone-H), 7.02-7.08 (m, 3H, ArH), 7.34-7.37 (m, 1H, ArH), 7.44-7.51 (m, 6H, ArH), 7.69 (d, 1H, *J*=16.4 Hz, =CH), 7.86 (d, 1H, *J*=16.4 Hz, =CH), 7.92 (d, 1H, *J*=7.6 Hz, benzene-H), 8.10 (d, 1H, *J*=10.8 Hz, tropone-H); MS (ES+): 355.2 $(M+H)^+$. Anal. Calcd for $C_{23}H_{18}N_2O_2$: C 77.95, H 5.12, N 7.90; Found: C 78.38, H 5.17, N 8.14.

(*E*)-3-(4-methoxystyryl)-1-phenylcyclohepta[c] pyrazol-8(1H)-one (2c)

IR (KBr) ν : 1630, 1593, 1552, 1521, 11488, 1391, 1341, 1262, 1200, 1110, 1070, 1010, 900, 793, 691 cm^{-1}; 1H NMR (CDCl3) δ : 3.80 (s, 3H, OMe), 6.89 (d, 1H, J=12.4 Hz, tropone-H), 6.96-7.00 (m, 3H, ArH), 7.41-7.53 (m, 6H, ArH), 7.56 (d, 1H, *J*=16.0 Hz, =CH), 7.61 (d, 1H, *J*=16.0 Hz, =CH), 7.72 (d, 2H, *J*=8.4 Hz, benzene-H), 8.11 (d, 1H, *J*=10.8 Hz, tropone-H); MS (ES+): 355.2 $(M+H)^+$. Anal. Calcd for $C_{23}H_{18}N_2O_2$: C 77.95, H 5.12, N 7.90; Found: C 78.27, H 5.04, N 8.14.

(E)-3-(4-chlorostyryl)-1-phenylcyclohepta[c]pyrazol-8(1H)-one (2d)

IR (KBr) ν : 1630, 1581, 1546, 1515, 1496, 1454, 1397, 1244, 1206, 1120, 1050, 1017, 974, 870, 748, 699 cm-1; 1H NMR (CDCl3) δ : 6.90 (d, 1H, *J*=12.4 Hz, tropone-H), 7.41-7.49 (m, 7H, ArH), 7.57 (d, 1H, *J*=16.4 Hz, =CH), 7.78-7.83 (m, 3H, ArH and =CH), 8.15 (d, 1H, *J*=10.8 Hz, tropone-H); MS (ES+): 359.2 $(M+H)^+$. Anal. Calcd for $C_{22}H_{15}ClN_2O$: C 73.64, H 4.21, N 7.81; Found: C 73.50, H 4.25, N 7.95.

(E)-3-(2-bromostyryl)-1-phenylcyclohepta[c]pyrazol-8(1H)-one (2e)

IR (KBr) ν : 1630, 1587, 1550, 1497, 1431, 1395, 1206, 1017, 961, 802, 771, 748 cm-1; 1H NMR (CDCl3) δ : 6.91 (d, 1H, *J*=12.4 Hz, tropone-H), 6.97-7.00 (m, 1H, ArH), 7.28-7.30 (m, 1H, ArH), 7.48 (d, 1H, *J*=15.9 Hz, =CH), 7.44 (d, 1H, *J*=15.9 Hz, =CH), 7.41-7.52 (m, 5H, ArH), 7.79-7.83 (m, 2H, ArH), 7.68 (d, 1H, *J*=8.0Hz, benzene-H), 8.12-8.15 (m, 2H, ArH); MS (ES+): 403.1, 405.1 $(M+H)^+$. Anal. Calcd for $C_{22}H_{15}BrN_2O$: C 65.52, H 3.75, N 6.95; Found: C 65.39, H 3.67, N 7.01.

(*E*)-3-(4-cyanostyryl)-1-phenylcyclohepta[c]pyrazol-

8(1H)-one (2f)

IR (KBr) ν: 1637, 1551, 1524, 1443, 1400, 1350, 1302, 1272, 1254, 1236, 1200, 1178, 1056, 1030, 971, 802, 775, 706 cm-1; 1H NMR (CDCl3) δ: 6.92 (d, 1H, *J*=12.5 Hz, tropone-H), 7.01-7.04 (m, 1H, ArH), 7.42-7.52 (m, 6H, ArH), 7.63 (d, 1H, *J*=16.1 Hz, =CH), 7.88 (d, 2H, *J*=8.3 Hz, benzene-H), 7.96-8.00 (m, 3H, ArH and =CH), 8.17 (d, 1H, *J*=11.0 Hz, tropone-H); MS (ES+): 350.2 $(M+H)^+$. Anal. Calcd for $C_{23}H_{15}N_3O$: C 79.07, H 4.33, N 12.03; Found: C 78.97, H 4.25, N 11.99.

(E)-3-(4-nitrostyryl)-1-phenylcyclohepta[c]pyrazol-8(1H)-one (2g)

IR (KBr) ν: 1634, 1588, 1546, 1497, 1472, 1388, 1349, 1257, 1205, 1139, 1104, 1050, 1019, 970, 805, 790, 761 cm-1; 1H NMR (CDCl3) δ: 6.92 (d, 1H, *J*=12.4 Hz, tropone-H), 7.01-7.03 (m, 1H, ArH), 7.42-7.49 (m, 5H, ArH), 7.52 (d, 1H, *J*=16.4 Hz, =CH), 7.70 (d, 1H, *J*=16.4 Hz, =CH), 8.03-8.06 (m, 1H, ArH), 8.07 (d, 2H, *J*=8.4 Hz, benzene-H), 8.19 (1H, d, *J*=11.2 Hz, tropone-H), 8.26 (d, 2H, *J*=8.4 Hz, benzene-H); MS (ES+): 370.2 $(M+H)^+$. Anal. Calcd for $C_{22}H_{15}BrN_2O$: C 71.54, H 4.09, N 11.38; Found: C 71.43, H 4.00, N 11.24.

4. Acknowledgement

We thank the Foundation of Liaoning Province Key Laboratory of Applied Chemistry (Grant No. 2008s001) for financial support.

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