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A facile synthesis of (*E*)-3-styryl-1-phenyl cyclohepta[*c*]pyrazol-8(1*H*)-ones

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Abstract A facile synthesis of some novel (*E*)-3-styryl-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-ones via the condensation reaction of 3-cinnamoyltropolones with phenylhydrazine is described. All the synthesized compounds were obtained in good yields of 62–69 % and their structures were characterized by IR, ^{1}H NMR, MS, and elemental analysis. This procedure offers easy access to tropone-fused pyrazole derivatives in short reaction times, and the products are achieved in good yields.

Keywords Tropone · Pyrazole · Condensation reaction · 3-Cinnamoyltropolone · Phenylhydrazine

Introduction

The pyrazole ring system, one of the most valuable nitrogen heterocycles, has been the subject of considerable research due to its usefulness in synthetic organic chemistry and also because of its pharmacological properties [1–5]. Especially, the important role of ring-fused pyrazoles in medicinal and pharmaceutical chemistry is indisputable and well reflected by a large number of recent publications [5–9], including some excellent reviews [10, 11]. As a consequence, over recent years great efforts have been devoted to the synthesis of interesting types of ring-fused pyrazole derivatives [12–16]. Most fused pyrazole compounds reported in the literature comprise a common heterocyclic ring moiety fused with a pyrazole ring, such as pyrimidopyrazole [9, 12], pyrazoloquinoline [13, 17], pyrazoloindole [18], benzofuropyrazole [19], pyridopyrazole [8, 20], and synthetic analogues thereof. However, there are very few reports in which the heterocyclic moiety is replaced with a tropone unit.

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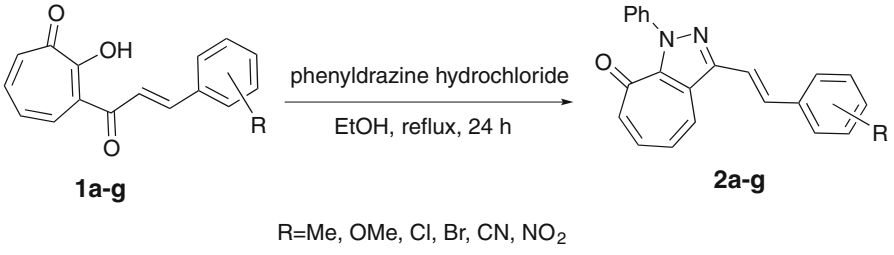
On the other hand, tropone natural products and synthetic tropone derivatives have attracted considerable interest due to the unique structure and properties of the tropone ring [21–23]. Recent studies have suggested that a combination of a heterocycle moiety fused with a tropone ring may increase their biological activities or create new medicinal properties [24–26]. For example, structural variations of established drugs with the tropone ring resulted in enhanced anticancer activity [26]. Therefore, there is much current interest in assembling a 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 [27–29].

In light of these findings, and in view of structural diversity playing a prominent role in medicinal and combinatorial chemistry for a faster and more efficient route towards new drug discovery [30], we assumed that incorporation of the tropone moiety instead of an aromatic or heteroaromatic ring fused with a pyrazole ring would be much more attractive and valuable for medicinal chemistry and drug discovery. Thus, the aim of the present work was to synthesize novel compounds combining these two systems in a molecular framework as in fused forms.

Results and discussion

Recently, we have reported the intramolecular oxidation cyclization reaction of 3-cinnamoyltropolone by the treatment with the I_2/DMSO/H_2SO_4 system for the synthesis of flavone-like tropones [31–33]. We have also developed an efficient synthesis of 5,7-dibromotropono[c]pyrazole derivatives via the condensation reaction of 3-acetyl-5,7-dibromotropolone with aromatic hydrazines [34]. In the context of our ongoing studies on troponoid chemistry and further extending the diversity of our previous work, we have become interested in the synthesis of novel 3-styryltropono[*c*]pyrazole derivatives (**2a**–**g**). Our strategy to reach this goal is outlined in Scheme 1. 3-Cinnamoyltropolones **1a**–**g** are easily synthesized in high yields and high purity as well as being based on our previous reported procedures [35].

Initially, we examined the reaction of **1a** 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 **1a** and phenylhydrazine hydrochloride was performed smoothly and gave the



Scheme 1 Synthesis of (*E*)-3-styryl-1-phenylcyclohepta[c]pyrazol-8(1*H*)-ones (**2a**–**g**)

desired (*E*)-3-(4-methylstyryl)-1-phenyltropono[*c*]pyrazole (**2a**) in good yield of 69 %. The reaction result we obtained is very similar to that reported by Lee et al. [36]. In addition, we also tried using 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.

As shown in Table 1, the effect of substituents on the benzene ring is not very strong, showing little distinction and giving about the same yields. For example, the troponyl-substituted chalcones **2a–c** (Entries 1–3) bearing electron-donating methyl and methoxy groups were obtained in 69, 65 and 66 % yields, respectively. On the other hand, compounds **2d–g** (Entries 4–7) bearing electron-withdrawing groups were obtained in the comparable yields of 62–67 %.

The structures of (*E*)-3-styryl-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-ones derivatives were deduced from their spectral data and elemental analysis as described for **2a**. The IR spectrum of reaction product **2a** showed a typical stretching vibration band at 1,636 cm^{-1} due to the tropone carbonyl group. The main features of its ^1H NMR spectrum showed a pair of AB doublets appearing at 7.47 and 7.69 ppm, consistent with the two vinylic protons with a large coupling constant $J = 16.0$ Hz, which indicated the expected *E*-configuration. 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 its molecular formula in accordance with the suggested molecular structure. The other synthesized compounds exhibited similar spectral characteristics except the substituents, which exhibited characteristic signals with appropriate chemical shifts. Additionally, it is worth noting that the structures of products **2** contain styryl group π-electron systems tethered to a pyrazole ring, which can be used as promising precursors for the synthesis of complex compounds, for example, via Diels–Alder reaction [37].

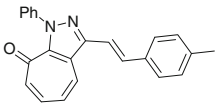
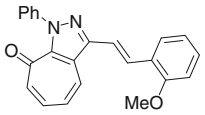
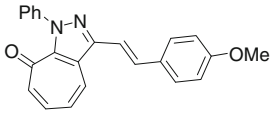
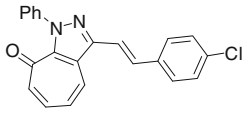
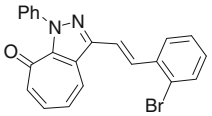
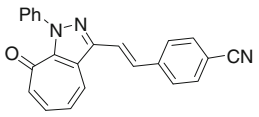
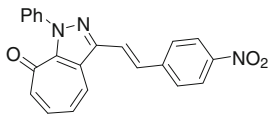
Conclusions

It can be concluded that the present investigation has demonstrated a facile synthesis of novel (*E*)-3-styryl-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-one derivatives. The molecules we have synthesized should allow us, in the future, to investigate structure–activity relationships over various biotests. Moreover, all these synthesized molecules can be used for the synthesis of more complex heterocyclic compounds, since a styryl group tethered to a pyrazole ring can be further elaborated, for example, via Diels–Alder reaction.

Experimental

The chemicals used in this work were obtained from Fluka and were used without purification. 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. The mass spectra

Table 1 Yields and physical properties of the compounds **2a–g**

Entry	Product	**2a–g**	Yield/%[a]	M.p./°C
1		**2a**	69	234–235
2		**2b**	65	203–205
3		**2c**	66	244–246
4		**2d**	64	216–218
5		**2e**	62	209–211
6		**2f**	67	225–227
7		**2 g**	63	238–240

[a] Isolated yields

were determined using a MSD VL ESI1 spectrometer. Elemental analyses were recorded on an Elementar vario EL-III element analyzer.

General procedure for synthesis (*E*)-3-styryl-1-phenylcyclohepta[*c*]pyrazol-8(1*H*)-one 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 and filtered to give the crude

products, which were further purified by recrystallization from acetic acid to afford products **2**. The yields and melting points are listed in Table 1 and the spectral and analytical data are given below.

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

Orange powder; IR (KBr, *v*, cm^{-1}): 1,636, 1,592, 1,557, 1,520, 1,496, 1,420, 1,400, 1,273, 1,214, 1,167, 1,148, 1,030, 1,014, 960, 896, 852, 801, 700; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 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 (ESI, *m*/*z*): 339.3 $[M + H]^+$. Anal. Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.24; H; 5.47; N, 8.35.

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

Yellow solid, IR (KBr, *v*, cm^{-1}): 1,610, 1,558, 1,519, 1,510, 1,476, 1,410, 1,255, 1,217, 1,025, 974, 761, 702; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 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 (ESI, *m*/*z*): 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(1*H*)-one (**2c**)

Yellow solid, IR (KBr, *v*, cm^{-1}): 1,630, 1,593, 1,552, 1,521, 1,1488, 1,391, 1,341, 1,262, 1,200, 1,110, 1,070, 1,010, 900, 793, 691; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 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 (ESI, *m*/*z*): 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, 8.09.

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

Yellow solid, IR (KBr, *v*, cm^{-1}): 1,630, 1,581, 1,546, 1,515, 1,496, 1,454, 1,397, 1,244, 1,206, 1,120, 1,050, 1,017, 974, 870, 748, 699; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 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, 5H, ArH and = CH), 8.15 (d, 1H, $J = 10.8$ Hz, tropone-H); MS (ESI, *m*/*z*): 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(1*H*)-one (**2e**)

Yellow solid, IR (KBr, *v*, cm^{-1}): 1,630, 1,587, 1,550, 1,497, 1,431, 1,395, 1,206, 1,017, 961, 802, 771, 748; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 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, $J = 8.0$ Hz, benzene-H), 8.12–8.15 (m, 2H, ArH); MS (ESI, *m/z*): 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(1*H*)-one (**2f**)

Yellow solid, IR (KBr, *v*, cm^{-1}): 1,637, 1,551, 1,524, 1,443, 1,400, 1,350, 1,302, 1,272, 1,254, 1,236, 1,200, 1,178, 1,056, 1,030, 971, 802, 775, 706; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 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 (ESI, *m/z*): 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(1*H*)-one (**2g**)

Yellow solid, IR (KBr, *v*, cm^{-1}): 1,634, 1,588, 1,546, 1,497, 1,472, 1,388, 1,349, 1,257, 1,205, 1,139, 1,104, 1,050, 1,019, 970, 805, 790, 761; ^1H NMR ($CDCl_3$, 400 MHz) (δ, ppm): 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 (d, 1H, $J = 11.2$ Hz, tropone-H), 8.26 (d, 2H, $J = 8.4$ Hz, benzene-H); MS (ESI, *m/z*): 370.2 $[M + H]^+$. Anal. Calcd for $C_{22}H_{15}N_3O_3$: C, 71.54; H, 4.09; N, 11.38. Found: C, 71.43; H, 4.00; N, 11.24.

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