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SYNTHESIS OF 5,7-DIBROMOTROPONO[*c*]PYRAZOLE DERIVATIVES

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Abstract –A facile synthesis of some novel 5,7-dibromotropono[*c*]pyrazole derivatives via the condensation reaction of 3-acetyl-5,7-dibromotropolone with aromatic hydrazines 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.

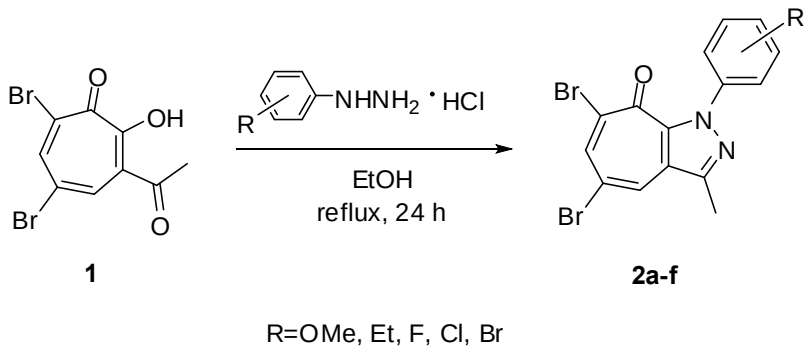
The pyrazole moiety is present in a wide variety of biologically active compounds.[1-3] Numerous compounds containing pyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory, antipyretic, antibacterial, hypoglycemic, sedative-hypnotic activity.[4-7] This class of compounds 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 addition, it is reported that the presence of bromo moieties on troponoid nucleus is reported to inhibit the Hepatitis C virus.[27]

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,[28] the synthesis of novel pyrazoles fused to bromo-substituted tropone ring would be much more attractive. To the best our knowledge, 3-acetyl-5,7-dibromomotropolone has been synthesized conveniently for many

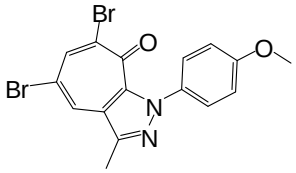
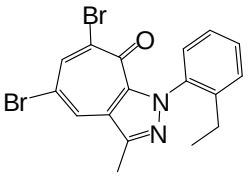
years.[29] However, further modification of it is very limited.[29] Thus, we are very interested in transforming 3-acetyl-5,7-dibromo-tropolone into some novel 5,7-dibromotropono[*c*]pyrazole derivatives, which should be useful precursors for achieving new biologically active tropolone compounds.

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,[30-36] herein, we wish to report the synthesis of 5,7-dibromo-3-methyl-1-aryltropono[*c*]pyrazoles (**2a-f**) by the reaction of 3-acetyl-5,7-dibromo-tropolone (**1**) with some substituted phenylhydrazine hydrochlorides as shown in Scheme 1. Initially, we examined the reaction of **1** with free (4-methoxyphenyl)hydrazine 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 (4-methoxyphenyl)hydrazine hydrochloride was performed smoothly to give the desired 5,7-dibromotropono[*c*]pyrazole (**2a**) in good yield of 70%. The reaction result we obtained is very similar to the literature reported by Lee *et al*.[37] 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.

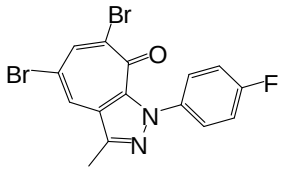
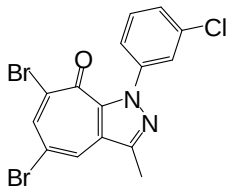
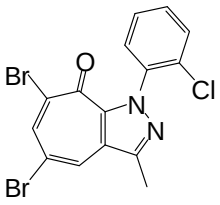
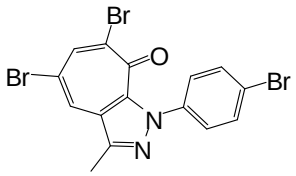


Scheme 1. Synthetic route of the title compounds **2a-f**

Table 1. Synthesis of 5,7-dibromotropono[*c*]pyrazole derivatives (**2a-f**)

Entry	Product		Yield (%)[a]
1		**2a**	70
2		**2b**	86

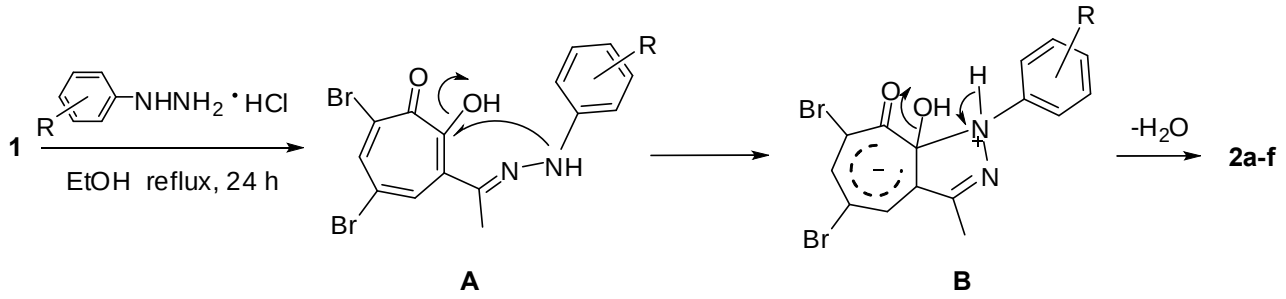
Continued (Table 1)

Entry	Product		Yield (%)[a]
3		**2c**	67
4		**2d**	74
5		**2e**	71
6		**2f**	88

[a]Isolated yield.

From Table 1, it seems that the electronic nature of the substituents has no significant effect on the reactions; all the tropono[*c*]pyrazoles with electron-donating (Entries 1 and 2) or electron-withdrawing (Entries 3-6) worked well and gave the corresponding title compounds in good to excellent yields, showing little distinction. The ease of isolation of all the products was notable; after aqueous work-up the products were isolated as the main products.

The formation of **2a-f** may be interpreted by the following proposed mechanism as shown in Scheme 2. Conversion of 3-acetyl-5,7-dibromotropolone (**1**) into the corresponding hydrazone derivative (**A**) and subsequent attack of the resulting hydrazone moiety at the hydroxyl carbon of tropolone ring formed a pyrazole ring system (**B**). After this cyclization, dehydration led to the formation of tropono[*c*]pyrazole ring **2a-f**.



Scheme 2. Possible mechanistic pathway of formation of the title compounds **2a-f**

The structures of all the new synthesized compounds were confirmed by spectral data and elemental analysis. For example, the IR spectrum of **2a** exhibited the absence of hydroxyl group at about 3180 cm^{-1} and the presence of one typical carbonyl absorptions for the tropone moieties at 1621 cm^{-1}. In the ^1H NMR spectrum of **2a**, the signals from two tropone hydrogens appeared as two doublet signals at 7.87 (d, 1H, J = 1.70 Hz) and 8.48 (d, 1H, J = 1.75 Hz), which arose a result of coupling to each other. The ESI-MS (positive-ion mode) exhibited a characteristic quasi-molecular ion peak cluster $(M+H)^+$ at *m/z* 423.02, 424.99, and 427.00 with a ratio of 1:2:1, indicating the presence of two Br-atoms in them. Finally, the structure assigned for this reaction product 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 5,7-dibromo-1-aryl-3-methyltropono[*c*]pyrazoles (**2a-f**) in good to excellent yields. 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 highly substituted tropolones since bromo group on tropone ring can be further elaborated to a variety of other functional groups, for example, via metal-catalyzed coupling reactions.

EXPERIMENTAL

Melting points (uncorrected) were determined by using WRS-1B melting points apparatus. The ^1H NMR spectra were recorded on a Brucker AVANCE 400 NMR spectrometer at 300 MHz using TMS as internal standard. The Mass spectra were determined using a MSD VL ESI1 spectrometer. The elemental analyses was performed for C, H, N using an Elementar Vario EL-III element analyzer. The progress of reactions was monitored by thin-layer chromatography (TLC) on silica gel GF254 using EtOAc/petroleum ether (1/3).

General procedure for the synthesis of 5,7-dibromo-1-aryl-3-methyltropono[*c*]pyrazoles (2a-f). To a solution of 3-acetyl-5,7-dibromotropolone **1** (0.32 g, 1 mmol) in 5 mL of EtOH was added the corresponding 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.

5,7-Dibromo-1-(4-methoxyphenyl)-3-methyltropono[*c*]pyrazole (2a). This compound was obtained as yellow solid, mp 116-117 °C. IR (KBr) ν/cm^{-1}: 3049, 2978, 1621 (C=O), 1582 (C=N), 1551, 1493, 1452, 1379, 1333, 1141, 1049, 1015, 879, 835; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.59 (s, 3H, Me), 3.86 (s, 3H, OMe), 6.97 (m, 2H, ben-H), 7.24 (m, 2H, ben-H), 7.87 (d, 1H, J = 1.70 Hz, tropone-H), 8.48 (d, 1H, J = 1.75 Hz, tropone-H); MS (ESI, *m/z*): 423.02, 424.99, 427.00 $(M+H)^+$; Anal. Calcd for $C_{16}H_{12}Br_2N_2O_2$: C, 45.31; H, 2.85; N, 6.61. Found: C, 45.10; H, 3.03; N, 6.39.

5,7-Dibromo-1-(2-ethylphenyl)-3-methyltropono[*c*]pyrazole (2b). This compound was obtained as yellow solid, mp 170-172 °C. IR (KBr) ν/cm^{-1}: 2965, 2868, 1619 (C=O), 1583 (C=N), 1542, 1495, 1450, 1381, 1328, 1124, 1085, 1016, 878, 855; ^{1}H NMR ($CDCl_3$) δ (ppm): 1.04 (t, 3H, J = 7.6 Hz, CH_3), 2.23 (q, 2H, J = 7.6 Hz, CH_2), 2.60 (s, 3H, Me), 7.35-7.41 (m, 3H, ben-H), 7.47 (d, 1H, J = 7.8 Hz, ben-H), 7.87 (d, 1H, J = 1.75 Hz, tropone-H), 8.49 (d, 1H, J = 1.75 Hz, tropone-H); MS (ESI, *m/z*): 421.01, 423.02, 425.03 $(M+H)^+$; Anal. Calcd for $C_{17}H_{14}Br_2N_2O$: C, 48.37; H, 3.34; N, 6.64. Found: C, 48.18; H, 3.47; N, 6.41.

5,7-Dibromo-1-(4-fluorophenyl)-3-methyltropono[*c*]pyrazole (2c). This compound was obtained as yellow solid, mp 210-212 °C. IR (KBr) ν/cm^{-1}: 1629 (C=O), 1588 (C=N), 1543, 1510, 1430, 1371, 1331, 1291, 1218, 1159, 1088, 1013, 856, 835; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.59 (s, 3H, Me), 7.13-7.16 (m, 2H, ben-H), 7.29-7.32 (m, 2H, ben-H), 7.88 (d, 1H, J = 1.75 Hz, tropone-H), 8.51 (d, 1H, J = 1.80 Hz, tropone-H); MS (ESI, *m/z*): 410.98, 412.99, 414.97 $(M+H)^+$; Anal. Calcd for $C_{15}H_9Br_2FN_2O$: C, 43.72; H, 2.20; N, 6.80. Found: C, 43.92; H, 2.02; N, 6.59.

5,7-Dibromo-1-(2-chlorophenyl)-3-methyltropono[*c*]pyrazole (2d). This compound was obtained as white solid, mp 208-209 °C. IR (KBr) ν/cm^{-1}: 1622 (C=O), 1584 (C=N), 1517, 1490, 1450, 1367, 1326, 1259, 1210, 1100, 1064, 1017, 879, 853; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.61 (s, 3H, Me), 7.39-7.45 (m, 3H, ben-H), 7.50 (d, 1H, J = 7.8 Hz, ben-H), 7.90 (d, 1H, J = 1.75 Hz, tropone-H), 8.51 (d, 1H, J = 1.70 Hz, tropone-H); MS (ESI, *m/z*): 426.94, 428.94, 430.94, 432.95 $(M+H)^+$; Anal. Calcd for $C_{15}H_9Br_2ClN_2O$: C, 42.04; H, 2.12; N, 6.54. Found: C, 41.86; H, 2.13; N, 6.40.

5,7-Dibromo-1-(3-chlorophenyl)-3-methyltropono[*c*]pyrazole (2e). This compound was obtained as yellow solid, mp 245-246 °C. IR (KBr) ν/cm^{-1}: 1621 (C=O), 1587 (C=N), 1545, 1486, 1446, 1378, 1331, 1292, 1199, 1103, 1024, 908, 858, 788; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.60 (s, 3H, Me), 7.19-7.21 (m, 1H, ben-H), 7.35-7.40 (m, 2H, ben-H), 7.43-7.45 (m, 1H, ben-H), 7.88 (d, 1H, J = 1.75 Hz, tropone-H), 8.51 (d, 1H, J = 1.75 Hz, tropone-H); MS (ESI, *m/z*): 426.97, 428.95, 430.97, 432.84 $(M+H)^+$; Anal. Calcd for $C_{15}H_9Br_2ClN_2O$: C, 42.04; H, 2.12; N, 6.54. Found: C, 41.90; H, 2.40; N, 6.33.

5,7-Dibromo-1-(4-bromophenyl)-3-methyltropono[*c*]pyrazole (2f). This compound was obtained as yellow solid, mp 220-222 ^{o}C. IR (KBr) ν/cm^{-1}: 1620 (C=O), 1584 (C=N), 1544, 1491, 1392, 1330, 1092, 1008, 856, 825; ^{1}H NMR ($CDCl_3$) δ (ppm): 2.59 (s, 3H, Me), 7.19-7.22 (m, 2H, ben-H), 7.57-7.60 (m, 2H, ben-H), 7.88 (d, 1H, J = 1.75 Hz, tropone-H), 8.51 (d, 1H, J = 1.75 Hz, tropone-H); MS (ESI, *m/z*): 470.90, 472.92, 474.88, 476.89 $(M+H)^+$; Anal. Calcd for $C_{15}H_9Br_3N_2O$: C, 38.09; H, 1.92; N, 5.92. Found: C, 37.92; H, 2.14; N, 5.78.

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