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# Tetrabutylammonium hydrogen sulfate mediated domino reaction: synthesis of novel benzopyran-annulated pyrano[2,3-c]pyrazoles

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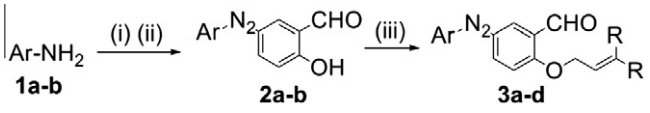
ABSTRACT

A tetrabutylammonium hydrogen sulfate (TBA-HS) mediated procedure for one pot synthesis of novel benzopyran-annulated pyrano[2,3-c]pyrazoles via domino/Knoevenagel-hetero-Diels–Alder reaction has been demonstrated.



Pyrano- and benzopyrano-fused heterocycles have attracted an increasing interest of many researchers because of their potential applications in medicinal chemistry. The compounds containing a pyrano[2,3-c]pyrazole unit have shown antimicrobial,[1] insecticidal,[2] anti-inflammatory,[3] and molluscicidal activity.[4] On the other hand, photochromic compounds having a benzopyrane nucleus have practical applications in the data storage, optical filters, displays, sensor protection, waveguides, and ophthalmic plastic lenses.[5] The 6-aminochromene, particularly, is a precursor to many bioactive compounds.[6] In view of this, it is of interest to develop the benzopyranopyran skeleton bearing amino group and its precursors. In the present work, an aryldiazenyl moiety has been introduced in a benzopyrano-fused pyrano[2,3-c]pyrazole unit giving a precursor to novel bioactive polyheterocyclic systems.

The domino/Knoevenagel-hetero-Diels–Alder (DKHDA) strategy represents one of the most powerful ways to construct pyrano- and benzopyrano-fused heterocycles.[7] Various catalysts such as Lewis acids,[8] EDDA,[9] copper(I) iodide,[10] bismuth(III) chloride,[11] indium(III) chloride,[12] lithium perchlorate,[13] triphenylphosphonium perchlorate,[14] zinc oxide,[7a] D-proline,[15] ionic liquids,[16] and pyridine[17] have been employed to promote this reaction. To the best of our knowledge, there exists no report on the use of quaternary ammonium salts as a phase transfer catalyst (PTC). TBA-HS is an acidic catalyst[18] and has been successfully employed in dehydration and ring closing step of Hantzsch dihydropyridine like transformations,[19] synthesis of 1,8-dioxo-octahydroxanthene,[20] N-alkylation of indole,[21] 3-aryl coumarins,[22] and flavones.[23]




1a-b 2a-b 3a-d

**Scheme 1.** Reagents and conditions: (i) $NaNO_2$, HCl, 0–5 °C; (ii) salicylaldehyde, NaOH, 0–5 °C; (iii) allyl or prenyl bromide, $K_2CO_3$, DMF, rt.

**Table 1**
Effect of catalyst and solvent on DKHDA reaction of **3a**/**3c** to **4a**

| Entry | Substrate | mol % of TBA-HS | Solvent (reflux) | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | **3a**/**3c** | — | Acetonitrile | 24 | — |
| 2 | **3a**/**3c** | — | Ethanol | 24 | — |
| 3 | **3a**/**3c** | — | Xylene | 24 | Trace |
| 4 | **3a**/**3c** | 10 | Acetonitrile | 24 | 10[a]/65[b] |
| 5 | **3a**/**3c** | 10 | Ethanol | 24 | 10[a]/35[b] |
| 6 | **3a**/**3c** | 10 | Xylene | 24 | 40[a]/43[b] |
| 7 | **3a** | 25 | Xylene | 9 | 82 |
| 8 | **3a** | 30 | Xylene | 9 | 80 |
| 9 | **3c** | 25 | Acetonitrile | 12 | 70 |
| 10 | **3c** | 30 | Acetonitrile | 12 | 70 |

[a] Product from substrate **3a**.
[b] Product from substrate **3c**.

The present work deals with TBA-HS mediated DKHDA reaction to afford some novel benzopyrano[4′,3′:4,5]pyrano[2,3-c]pyrazoles from substituted salicylaldehydes (**3a**–**d**) and 5-pyrazolones

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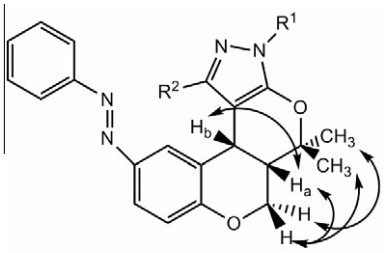
**Table 2**
Synthesis of chromeno[4′,3′:4,5]pyrano[2,3-c]pyrazoles

| Entry | Product | Ar | R | $R^1$ | $R^2$ | Time (h) | Yield (%) | MP[a] (°C) |
|---|---|---|---|---|---|---|---|---|
| 1 | **7a** | Ph | H | Ph | Me | 9 | 82 | 190–192 |
| 2 | **7b** | Ph | H | *p*-MePh | Me | 8 | 85 | 179–181 |
| 3 | **7c** | Ph | H | *m*-ClPh | Me | 8 | 84 | 189–192 |
| 4 | **7d** | Ph | H | Ph | Ph | 11 | 78 | 203–206 |
| 5 | **7e** | *p*-ClPh | H | Ph | Me | 10 | 85 | 218–220 |
| 6 | **7f** | *p*-ClPh | H | *p*-MePh | Me | 7 | 80 | 175–176 |
| 7 | **7g** | *p*-ClPh | H | *m*-ClPh | Me | 8 | 88 | 180–182 |
| 8 | **7h** | *p*-ClPh | H | Ph | Ph | 10 | 80 | 210–213 |
| 9 | **7i** | Ph | Me | Ph | Me | 11 | 70 | 177–179 |
| 10 | **7j** | Ph | Me | *p*-MePh | Me | 10 | 75 | 154–156 |
| 11 | **7k** | Ph | Me | *m*-ClPh | Me | 8 | 74 | 187–189 |
| 12 | **7l** | Ph | Me | Ph | Ph | 12 | 68 | 170–174 |
| 13 | **7m** | *p*-ClPh | Me | Ph | Me | 10 | 79 | 180–182 |
| 14 | **7n** | *p*-ClPh | Me | *p*-MePh | Me | 9 | 83 | 200–203 |
| 15 | **7o** | *p*-ClPh | Me | *m*-ClPh | Me | 8 | 80 | 197–200 |
| 16 | **7p** | *p*-ClPh | Me | Ph | Ph | 11 | 72 | 190–192 |

[a] Uncorrected.




**7i** $R^1$= Ph, $R^2$= Me
**7j** $R^1$= *p*-MePh, $R^2$= Me

**Figure 1.** Characteristic NOE's of **7i** and **7j**.

(**4a–d**). The products, thus obtained via this cascade sequence are interesting substrates and may possess some bioprofiles. Substituted salicylaldehydes **3a–d** were prepared[9c,24] from aryldiazenyl salicylaldehydes **2a–b** and allyl or prenyl bromide in dry DMF in the presence of anhydrous $K_2CO_3$ at room temperature (Scheme 1). Substrates **2a–b** were prepared by a known coupling reaction.[25]

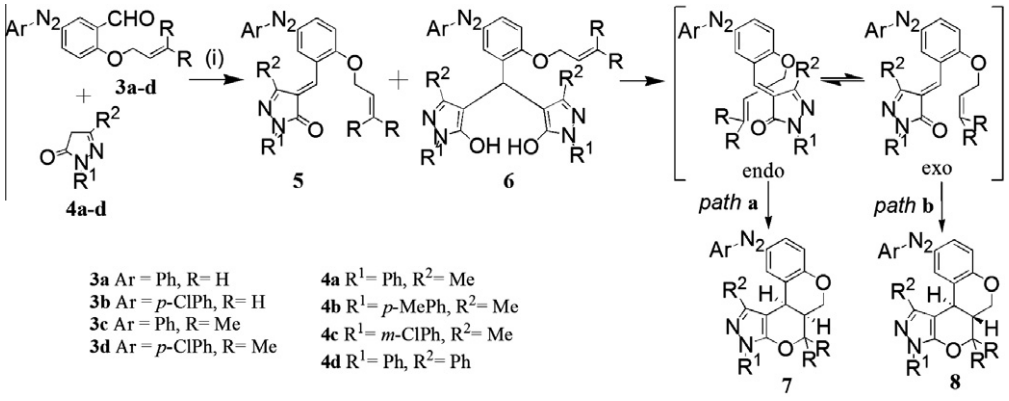
DKHDA reaction of the compound **3a**/**3c** to **4a** was used as a model to optimize the condition. The experimental results are summarized in Table 1.

As a first case, we examined the catalyst-free domino reaction of substrates **3a**/**3c** to **4a** by refluxing the substrates in acetonitrile, ethanol, and xylene for 24 h (entries 1, 2 and 3, respectively). A trace amount of cyclized product was obtained when xylene was used (entry 3) and no product formation was observed with the other two solvents. When we employed TBA-HS as a catalyst, we noticed an improvement in the yields from both the substrates **3a** and **3c**. In the presence of 10 mol % TBA-HS, the substrate **3a** gave 40% yield of the cyclized product under xylene reflux (entry 6), while the substrate **3c** gave 65% yield under acetonitrile reflux (entry 4). Catalyst loading of 25 mol % was found to be optimal to afford the cycloadduct in higher yields (entries 7 and 9). The optimized conditions[26] were applied to obtain other domino products **7a–p** (Table 2).

The spectroscopic data[27] of all the compounds **7a–p** are in good agreement with their proposed *cis*-fused geometry. The $^1$H NMR showed a doublet in $\delta$ 4.2–4.8 ppm range ($J$ = 4–5 Hz) which is attributed to $H_b$ proton and multiplets in $\delta$ 2.2–2.8 ppm range assignable to $H_a$. Furthermore, the nuclear Overhauser effect spectroscopy (NOESY) and the double quantum filtered correlation spectroscopy (DQFCOSY) data support the proposed structures of **7i** and **7j** (Fig. 1).

A probable mechanism is presented in Scheme 2. The reaction proceeds through simultaneous generation of two intermediates, a Knoevenagel adduct **5** and Knoevenagel–Michael adduct[28] **6** (Scheme 2). They are the common products obtained in TBA-HS mediated reaction. It proceeds with an attack of an acid catalyst on pyrazolone **(4a–d)** generating a reactive tetrabutylammonium pyrazolonate. It then reacts with aldehyde substrates **(3a–d)** to form the intermediates, **5** and **6**. The spectroscopic data[29] of **6k** are in good agreement with its proposed structure. Under the influence of heat, light, or long time storage, it was converted into intermediates **5k** and **4c** (Scheme 3). When compound **6k** was subsequently refluxed, it gave cycloadduct **7k**. Thus, it was concluded that the initially formed Michael adduct gets converted into the Knoevenagel intermediate on subsequent reflux.

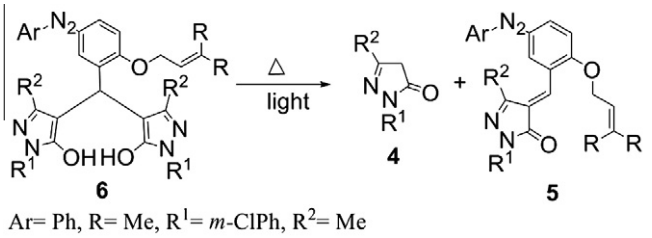
The stereochemistry of the reaction can be predicted by the *endo*- and *exo*- orientations of the dienophile. There are four possible transition structures namely, *exo-E-anti*, *endo-Z-anti*, *endo-E-*



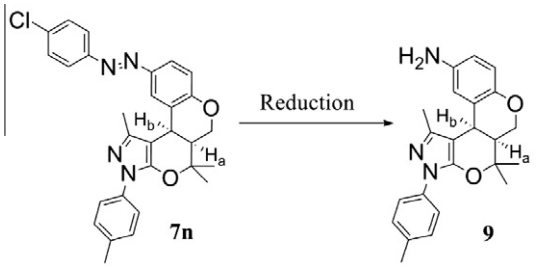

**3a** Ar = Ph, R= H
**3b** Ar = *p*-ClPh, R= H
**3c** Ar = Ph, R= Me
**3d** Ar = *p*-ClPh, R= Me

**4a** $R^1$= Ph, $R^2$= Me
**4b** $R^1$= *p*-MePh, $R^2$= Me
**4c** $R^1$= *m*-ClPh, $R^2$= Me
**4d** $R^1$= Ph, $R^2$= Ph

**Scheme 2.** Reagents and conditions: (i) TBA-HS (25 mol %), xylene or acetonitrile, reflux.




**Scheme 3.** Effect of light or heat on stability of compound **6k**.




**Scheme 4.** The reduction of diazenyl group and formation of amino benzopyrane **9**.

*syn,* and *exo-Z-syn.*[7h] The $^1$H NMR study showed that the reaction product is mainly of its *cis*-isomeric form even though the two pathways (a and b) are possible (Scheme 2). Allyl moiety based substrates required higher temperature compared to the one containing prenyl moiety. These observations are well supported by the fact that the HOMO–LUMO gap[30] for diene and dienophile interaction is relatively less in the case of prenyl moiety. Therefore, it is assumed that the interaction of prenyl dienophile is more favorable.[7f]

As part of our preliminary studies, we could isolate the aminochromene **9** by reducing **7n** (Scheme 4). The formation of this novel product **9** has been confirmed by spectroscopic data.[31]

In summary, we have described a one pot synthesis of novel chromeno[4′,3′:4,5]pyrano[2,3-c]pyrazoles, by TBA-HS mediated DKHDA reaction. The advantages of this methodology are the easy work-up procedure, high stereoselectivity and isolation of the product in high yield with excellent purity. Furthermore, TBA-HS is a nontoxic, noncorrosive, commercially available, and inexpensive catalyst.

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.108.

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24. *General procedure for the synthesis of substituted benzaldehydes* **3a–d***:* To a stirred solution of **2** (0.01 mol) with anhydrous potassium carbonate (0.015 mol) in DMF (25 ml), a solution of allyl bromide (0.015 mol) or prenyl bromide (0.015 mol) in DMF (5 ml), was added drop-wise. The reaction mixture was stirred at room temperature till the completion of the reaction as confirmed by the TLC (10–12 h). The resulting mass was then poured into 100 g of ice with constant stirring. The solid residue was filtered, washed with cold water (3 × 10 ml), and dried at room temperature. The products **3a–d** were obtained quantitatively with an excellent purity.
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26. *General procedure for the synthesis of benzopyran-annulated pyrano[2,3-c]pyrazoles (***7a–p***):* A mixture of aldehydes **3a–d** (2 mmol), pyrazolones **4a-d** (2 mmol) and catalyst TBA-HS (25 mol %) was stirred under refluxing xylene (when R = H) or acetonitrile (when R = $CH_3$) for a specified time shown in Table 2. After complete conversion, as indicated by the TLC, the mixture was cooled and subjected to reduced pressure to remove solvent. The residue **7a–p** were washed with an appropriate solvent such as xylene or acetonitrile to remove any residual starting material and dried in vacuo. The products were obtained in 68–88% yields. Analytically pure sample was obtained by preparative TLC using ethyl acetate/hexane (3:7) as an eluent.
27. *Spectroscopic data of some selected compounds:* Compound **7a**:Yellow solid, mp 190–192 °C; IR (KBr): $\nu_{max}$ ($cm^{-1}$) 2957, 2927, 1490, 1467, 1241, 1092, 1026, 831, 758; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.58 (s, 3H, 5-$CH_3$ ax), 1.60 (s, 3H, 5-$CH_3$ eq), 2.43 (s, 4H, 1-$CH_3$), 2.60 (m, 1H, 5a-H), 4.18 (t, $J$ = 10.4 Hz, 1H, 6-H ax), 4.33 (d, $J$ = 4.8 Hz, 1H, 11b-H), 4.47 (m, 2H, 5-H), 4.66 (dd, $J$ = 8.0 Hz, $J$ = 2.4 Hz, 1H, 6-H eq), 6.99 (d, $J$ = 8.8 Hz 1H, 8-H), 7.22–7.87 (m, 11H, Ar–H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 14.41, 29.51, 30.12, 66.20, 68.52, 99.48, 118.11, 120.29, 122.76, 123.63, 125.15, 125.66, 126.01, 129.55, 129.86, 131.34, 138.65, 145.11, 146.49, 146.77, 148.09, 149.24, 149.95, 152.40, 152.81; ESI-MS: $m/z$: 423.1 $(M+H)^+$; Compound **7d**: Yellow solid, mp 187–189 °C; IR (KBr): $\nu_{max}$ ($cm^{-1}$) = 3080, 3000, 2900, 1600, 1250, 1090, 850, 780, 675; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 1.60 (s, 3H, 5-$CH_3$ ax), 1.62 (s, 3H, 5-$CH_3$ eq), 2.26 (br s, 4H, 1-$CH_3$ and 5a-H), 4.09 (t, $J$ = 11.0 Hz, 1H, 6a-H), 4.30 (d, $J$ = 4.0 Hz, 1H, 11b-H), 4.54 (dd, $J$ = 8.4 Hz, $J$ = 3.2 Hz, 1H, 6H eq), 6.96 (d, $J$ = 8.4 Hz, 1H, 8-H), 7.25–8.07 (m, 11H, Ar–H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 15.01, 25.46, 26.26, 30.35, 38.08, 63.60, 81.76, 94.85, 117.37, 118.46, 120.57, 120.97, 122.62, 123.98, 125.87, 126.78, 128.10, 129.07, 130.06, 130.48, 131.49, 134.75, 146.13, 148.02, 152.96, 156.45; ESI-MS: $m/z$: 487.1 $(M+H)^+$; Compound **7h**: Yellow solid, mp 210–213 °C; IR (KBr): $\nu_{max}$ ($cm^{-1}$) = 2924, 1489, 1446, 1249, 1094, 1031, 877, 759; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 2.74 (m, 1H, 5a-H), 4.32 (t, $J$ = 11.4 Hz, 1H, 6-H ax), 4.55 (m, 2H, 5-H), 4.62 (dd, $J$ = 7.2 Hz, $J$ = 3.6 Hz, 1H, 6-H eq), 4.74 (d, 1H, $J$ = 4.8 Hz, 11b-H), 6.90 (d, $J$ = 8.4 Hz, 1H, 8-H), 7.25–8.02 (m, 15H, Ar–H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 30.67, 30.95, 66.62, 67.88, 98.28, 117.45, 120.95, 121.44, 123.81, 123.90, 124.01, 125.63, 126.12, 127.17, 128.21, 128.89, 128.94, 129.10, 130.21, 134.40, 136.10, 138.48, 147.22, 148.79, 149.72, 150.87, 154.75;

ESI-MS: $m/z$: 520.1 $(M+H)^+$; Compound **7j**: Yellow solid, mp 154–156 °C; IR (KBr): $\nu_{max}$ ($cm^{-1}$) = 3030, 3000, 2900 1580, 1245, 1090, 825, 750, 680; $^1H$ NMR (400 MHz, $CDCl_3$):$\delta$ 1.57(s, 3H, 5-$CH_3$ ax), 1.58 (s, 3H, 5-CH3 eq), 2.24 (br d, 4H, 1-$CH_3$ & 5a-H), 2.38 (S, 3H, $p$-$CH_3$), 4.10 (t, $J$ = 12.0 Hz, 1H, 6a-H), 4.30(d, $J$ = 4.4 Hz, 1H, 11b-H), 4.51 (dd, $J$ = 8.4 Hz, $J$ = 3.2 Hz, 1H, 6H eq), 6.95 (d, $J$ = 8.4 Hz, 1H, 8-H), 7.21–8.09 (m, 11H, Ar–H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 15.38, 20.95, 25.52, 26.07, 30.57, 38.23, 63.72, 80.63, 95.70, 117.21, 120.67, 121.62, 122.63, 123.61, 127.14, 129.07, 129.49, 130.38, 135.35, 146.04, 147.05, 147.60, 148.89, 152.81, 156.61; ESI-MS: $m/z$: 518.9 $(M+H)^+$.

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29. *Compound* **6k**: Yellow solid, mp 172 °C; IR (KBr): $\nu_{max}$ ($cm^{-1}$) = 3470, 3050, 2930, 1650, 1480, 1250, 1130, 830, 750, 690; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$ 1.76 (s, 3H, $CH_3$), 1.80 (s, 3H, $CH_3$), 2.27 (s, 6H, $CH_3$ of pyrazolone), 4.69 (d, $J$ = 6.4 Hz, 2H, O-$CH_2$), 5.17 (s, 1H, –CH═C–), 5.46 (s, 1H), 7.17–8.20 (m, 16H, Ar–H), 12.53 (br s, 1H, 5-OH of pyrazolone), 13.83 (s, 1H, 5-OH of pyrazolone); $^{13}C$ NMR (100 MHz, DMSO-$d_6$): $\delta$ 18.45, 25.95, 28.41, 65.52, 110.77, 112.73, 119.88, 122.49, 123.44, 124.04, 124.65, 125.61, 127.67, 128.31, 129.84, 130.54, 130.85, 131.02, 131.93, 132.30, 139.18, 146.02, 146.58, 152.69, 158.83.
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31. *Compound* **9**: White solid, mp 150–152 °C; IR (KBr): $\nu_{max}$ ($cm^{-1}$) = 3400, 3035, 2900, 1660, 1230,1050, 800, 750; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 1.42 (s, 3H, 5-$CH_3$ ax), 1.45 (s, 3H, 5-$CH_3$ eq), 2.11 (s, 3H, 1-$CH_3$), 2.20 (m, 1H, 5a-H), 2.30 (s, 3H, $p$-$CH_3$), 3.76 (t, $J$ = 10.2 Hz, 1H, 6a-H), 4.01 (d, $J$ = 4.4 Hz, 1H, 11b-H), 4.30 (dd, $J$ = 8.4 Hz, $J$ = 3.2 Hz, 1H, 6H eq), 4.83 (br s, 2H, $NH_2$), 6.62–6.69 (m, 11H, Ar–H), 7.22 (d, $J$ = 8 Hz, 2H, Ar–H), 7.52(d, $J$ = 8 Hz, 2H, Ar–H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ 15.58, 20.91, 25.09, 26.33, 29.97, 38.33, 63.22, 81.83, 96.82, 125.28, 116.58, 117.28, 120.31, 122.50, 129.92, 134.95, 136.64, 141.22, 145.20, 146.59, 147.94; ESI-MS: $m/z$: 376.1 $(M+H)^+$.