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# Cycloaddition of a 1,2-diaza-1,3-butadiene to phenylpropiolic acid: an efficient route to pyridazinoquinolone derivatives

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**Abstract**—Diazocoupling of dihydroquinolin-4-ones with aryldiazonium nitrates gave the corresponding diazo derivatives, which undergo facile (4+2) cycloaddition reactions with phenylpropiolic acid to afford 2-aryl-4a-methyl-10-oxo-4-phenyl-2,4a,5,10-tetrahydropyridazino[4,3-*b*]quinoline-3-carboxylic acid derivatives **3**. However, with β-nitrostyrene a mixture of three isomeric products **4a**–**c** was obtained.


Hetero Diels–Alder methodology has been extensively utilized for the synthesis of a variety of fused heterocycles.[1] Thus, a number of mono- and diaza-1,3-butadienes have been shown to be useful precursors to fused heterocycles; their cycloadditions are not confined to electron-rich dienophiles, through inverse-electron-demand Diels–Alder reactions, but also include electron-deficient dienophiles.[2,3] Heterodienes derived from π-deficient heteroaromatic compounds have been employed less frequently in such cycloaddition reactions.[3–6] We report herein the reaction of 1,2-diaza-1,3-butadienes **2**, generated by diazocoupling of quinolin-4-ones with aryldiazonium nitrates, with phenylpropiolic acid to afford 2-aryl-4a-methyl-10-oxo-4-phenyl-2,4a,5,10-tetrahydropyridazino[4,3-*b*]quinoline-3-carboxylic acid derivatives (**3**, Scheme 1).

Thus, 2-methylquinolin-4-ones undergo facile electrophilic substitution at C-3 on reaction with aryldiazonium salts generated in situ by reaction of anilines with amyl nitrate and HCl to furnish 1,2-diaza-1,3-butadiene systems **2**, which in turn undergo (4+2) cycloaddition reactions with phenylpropiolic acid to afford pyridazinoquinoline derivatives **3**. The crude products were subjected to column chromatography using hexane–ethyl acetate (3:1, silica gel 200–400 mesh) to give the pure products in 58–96% yields (Table 1).

The assigned structures are based on detailed spectral analysis.[7] The formation of 1:1 adducts was indicated by mass spectra, for example, the molecular ion peak for **3a** at *m*/*e* 409;[7] and corroborated by microanalytical data. The $^1$H NMR spectra[7] revealed, inter alia, that the methyl group is attached to a saturated carbon and shows an NOE on saturation of the proton resonances of the neighboring aromatic ring, thereby, confirming the regiochemistry of addition. Further, the carboxylic acid proton resonance is shifted downfield in the adduct, which is possibly attributable to intramolecular H-bonding with the aryl ring. When the spectra were run in DMSO-$d_6$ containing a small quantity of $D_2O$ the signal at $\delta$ 12.3 decreased gradually with time.[7] The reaction is analogous to the 1,3-dipole addition to a dipolarophile and the HOMO ($\psi_2$) of the 1,3-dipole and LUMO ($\pi^*$) of the interacting dipolarophile, which are *anti*-symmetric with respect to *m*-plane symmetry and therefore can undergo facile concerted cycloaddition.

The 1,2-diaza-1,3-butadiene systems **2** also underwent (4+2) cycloaddition with β-nitrostyrene to afford a mixture of three isomeric products **4a**–**c** (Scheme 2). The

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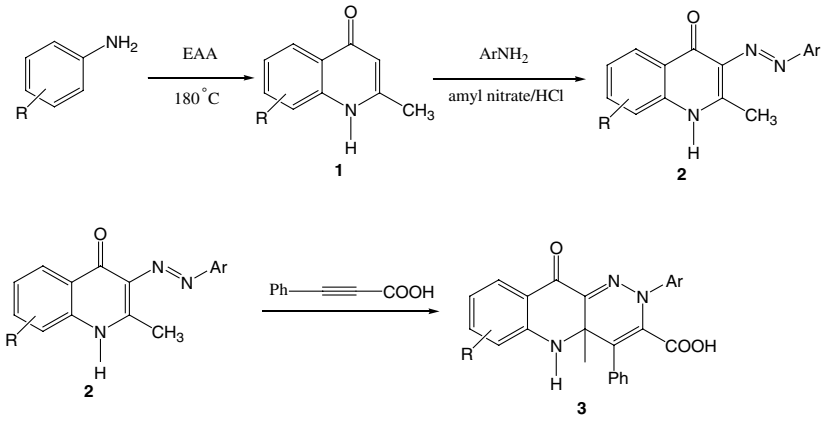


**Scheme 1.**

**Table 1.** Reaction times, yield (%) and mp's of the products

| Product | Ar | R | Reaction time (h) | %Yield | Mp (°C) |
|---|---|---|---|---|---|
| **3a** | $C_6H_5$ | H | 8 | 92 | 130 |
| **3b** | *m*-$NO_2C_6H_4$ | H | 6 | 84 | 136 |
| **3c** | *p*-$NO_2C_6H_4$ | H | 6 | 68 | 137 |
| **3d** | $C_6H_5$ | *p*-$NO_2$ | 8 | 94 | 143 |
| **3e** | *m*-$NO_2C_6H_4$ | *p*-$NO_2$ | 4 | 96 | 145 |
| **3f** | *p*-$NO_2C_6H_4$ | *p*-$NO_2$ | 6 | 62 | 149 |
| **3g** | $C_6H_5$ | *m*-$NO_2$ | 6 | 86 | 141 |
| **3h** | *m*-$NO_2C_6H_4$ | *m*-$NO_2$ | 8 | 75 | 143 |
| **3i** | *p*-$NO_2C_6H_4$ | *m*-$NO_2$ | 10 | 58 | 147 |

crude products were subjected to column chromatography using hexane–chloroform (5:11, silica gel 200–400 mesh) to give the pure products.

The assigned structures are based on detailed spectral analysis. The $^1$H NMR spectra[8] revealed, inter alia, that the methyl group is attached to a saturated carbon and showed an NOE on saturation of the proton resonance of the neighboring aromatic ring analogous with compound **2**. An identical observation was exhibited by both **4a** and **4b**. However, **4c** did not exhibit this effect showing that, in **4c** the methyl does not interact with the phenyl protons. Further, the relative yields of **4a**–**c** could be attributable to steric hindrance in the formation of **4b** and **4c**, thereby reducing their yields. The $^{13}$C NMR spectra of **4a** and **4b** clearly revealed the arrangement of nitro and phenyl groups with respect to the azo grouping. We are unsure why the *trans* product **4a** is formed predominantly rather then the *cis* product **4c**. Perhaps the nitro group with respect to the hydrogen of the neighboring phenyl ring might be playing a major role in the preference order.

Quinoline derivatives are widely employed in pharmaceutical industries for their potential application against various microorganisms; however, few pyridazines have been used in the pharmaceutical industry. Some selected derivatives of **3** (based on their solubility in DMSO) were screened for their potential anti-microbial activity and some exhibited significant activity against *C. albicans*, *S. aureus* and *E. coli*. Work is in progress to synthesize suitable analogues that are more active and then to study structure–activity relationships.

## References and notes

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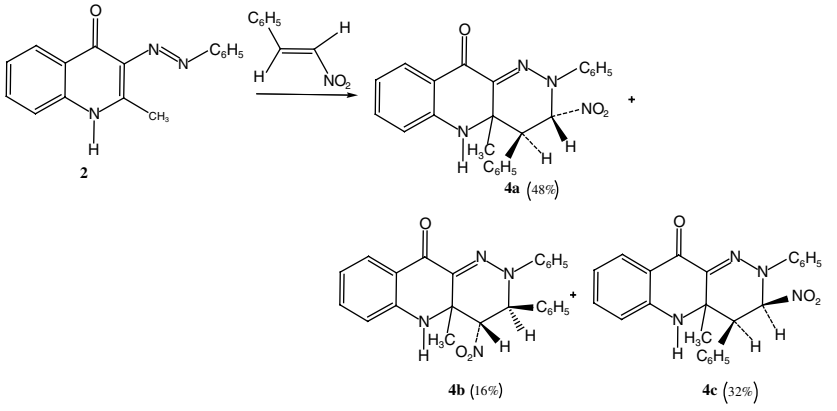


**Scheme 2.**

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7. Data for **3a**: mass (*m*/*z*) 409 ($M^+$), 336, 44, 77, 28. $^1$H NMR (300 MHz in $CDCl_3$, TMS at 0 ppm): $\delta$ 1.62 (d, 3H, $J = 6$ Hz), 6.11 (t, 1H, $J = 2.8$ Hz), 6.40 (s, 1H), 7.23–8.26 (m, 11H), 9.21 (t, 1H, $J = 8$ Hz), 12.31 (s, 1H). IR (KBr) $\nu_{max}$: 1350, 1658, 1672, 2100, 3250 cm$^{-1}$. Anal. Calcd for $C_{25}H_{19}N_3O_3$: C, 73.34; H, 4.68; N, 10.26. Found: C, 73.16; H, 4.67; N, 10.27.
8. Data for **4a**: $^1$H NMR (300 MHz in $CDCl_3$, TMS at 0 ppm): $\delta$ 1.22 (d, 3H, $J = 8$ Hz), 3.21 (d, 1H, $J = 12$ Hz), 5.32 (d, 1H, $J = 12$ Hz), 6.41–8.03 (m, 15H, ArH). $^{13}$C NMR (300 MHz in $CDCl_3$): $\delta$ 16.3, 44.2, 106.4, 120.0–140.8, 153.2, 189.1. IR (KBr) $\nu_{max}$: 1350, 1648, 2100 cm$^{-1}$. Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.82; H, 4.88; N, 13.51. Compound **4b**: $^1$H NMR (300 MHz in $CDCl_3$, TMS at 0 ppm): $\delta$ 1.21 (s, 3H), 3.90 (d, 1H, $J = 12$ Hz), 4.63 (d, 1H, $J = 10$ Hz), 6.44–8.01 (m, 15H, ArH). $^{13}$C NMR (300 MHz in $CDCl_3$): 17.0, 57.2, 97.1, 120.0–140.5, 154.2, 187.4. IR (KBr) $\nu_{max}$: 1648, 1350, 2100 cm$^{-1}$. Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.84; H, 4.91; N, 13.54. Compound **4c**: $^1$H NMR (300 MHz in $CDCl_3$, TMS at 0 ppm): $\delta$ 1.22 (d, 3H, $J = 8$ Hz), 3.05 (d, 1H, $J = 8$ Hz), 5.61 (d, 1H, $J = 8$ Hz), 6.42–8.07 (m, 15H, ArH). IR (KBr) $\nu_{max}$: 1658, 1672, 3250, 1350, 2100 cm$^{-1}$. Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.87; H, 4.89; N, 13.54.