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Synthesis of Tetrahydropyrazolo[4',3':5,6]pyrano[3,4-c]quinolones by Domino Knoevenagel/Hetero Diels–Alder Reactions

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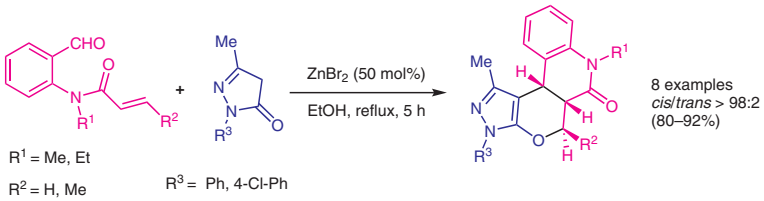

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Abstract An efficient Lewis acid mediated domino Knoevenagel/hetero Diels–Alder (DKHDA) reaction of pyrazolone derivatives with *N*-acrylated anthranilic aldehydes was developed, which afforded functionalized tetracyclic tetrahydropyrazolo[4',3':5,6]pyrano[3,4-c]quinolones. The products were formed in good yields and with excellent regio- and stereoselectivity in favor of the cis-configured isomer.

Key words domino reaction, regioselectivity, cyclizations, heterocycles, Diels–Alder reaction, Knoevenagel reaction

Domino reactions represent an important tool in organic chemistry.[1a] In this context, domino Knoevenagel/hetero Diels–Alder (DKHDA) reactions are of special interest as they proceed by formation of two or more rings in only one synthetic step.[1] Tetra- and pentacyclic heterocycles, containing a pyran or chroman moiety, have been synthesized through DKHDA reactions of internal *O*-allylated- and *O*-propargylated salicylic aldehydes with 1,3-dicarbonyl compounds.[2] There have also been reported DKHDA reactions of 2-formylphenyl-*N*-alkyl-2-phenylethenesulfonamides and 2-formylphenyl-2-phenylethenesulfonates for the synthesis of annelated benzosultams or benzosultones, respectively.[3] Furthermore, DKHDA reactions of *O*-acrylated salicylic aldehydes and 1,3-dicarbonyl or thiocarbonyl compounds allow the synthesis of polycyclic dihydrocoumarines.[4] We have recently reported the DKHDA reaction of *N*-acrylated anthranilic aldehydes and indolin-2-thiones, which provides a convenient access to pentacyclic 3,4-dihydroquinolones.[5]

The pyrazole moiety represents an important heterocyclic core structure because of its presence in many biologically active compounds,[6] pharmaceuticals,[7] agrochemicals,[8] and natural products.[9] Among pyrazole derivatives, Viagra®,[10] Celebrex®,[11] Acomplia®,[12] and Fipronil®[13] are commercial drugs. Pyrazoles display antimicrobial,[14] antitubercular,[15] antitumor,[16] anticancer,[17] and antihyperglycemic activities, and also inhibit IL-1 synthesis and HIV-1 reverse transcriptase.[18] Likewise, tetrahydropyranopyrazoles represent an important core structure because of their presence in various biologically active compounds (Figure 1, top).[19] On the other hand, functionalized 3,4-dihydroquinolone structures are privileged scaffolds that can be found in many synthetic and natural products (Figure 1, bottom).[20] They show cardiovascular effects and also exhibit phosphodiesterase inhibitory and anti-inflammatory ac-

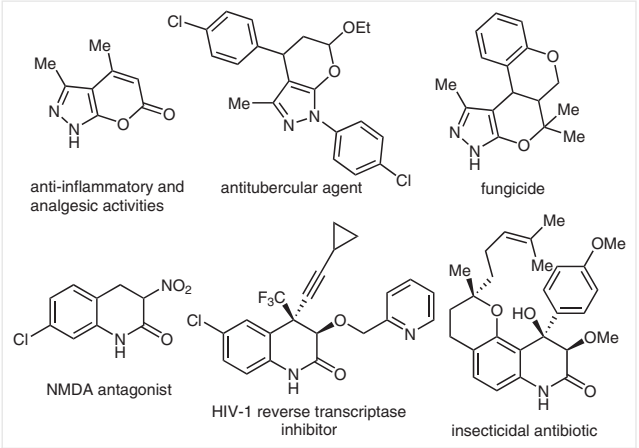

Figure 1 Biologically active annulated pyrazoles (top) and 3,4-dihydroquinolones (bottom)

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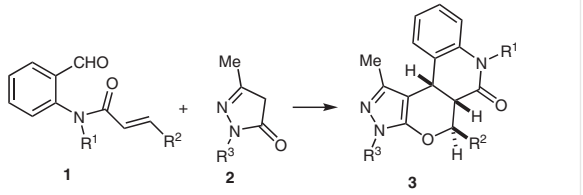
tivities.[21] 3,4-Dihydroquinolones have been prepared by Skraup–Doebner–von Miller reactions,[22] Friedlander–Friedel–Crafts cyclizations,[23] radical-mediated reactions,[24] oxidative cyclizations,[25] photochemical reactions,[26] transition-metal-catalyzed reactions,[27] and asymmetric synthetic approaches.[28]

An important concept in medicinal chemistry relies on the synthesis of hybrid molecules containing a combination of known pharmacophores.[29] Tetrahydropyrazolo[4',3':5,6]-pyrano[3,4-*c*]quinolones combine the structural units of pyrazoles, tetrahydropyranopyrazoles, and 3,4-dihydroquinolones as pharmacophoric core structures. This type of molecule has, to the best of our knowledge, not been reported in the literature so far. Following our general interest in the development of new synthetic methods and their application in heterocyclic chemistry,[30] we herein wish to report a new and convenient synthesis of tetrahydropyrazolo[4',3':5,6]pyrano[3,4-*c*]quinolones **3** by DKHDA reaction of pyrazolones **2** with *N*-acrylated anthranilic aldehydes **1** (Scheme 1).

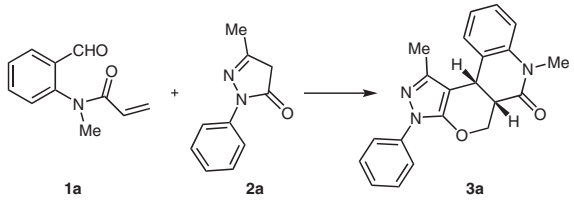


Scheme 1 DKHDA reaction of *N*-acrylated anthranilaldehydes with pyrazolones

N-Acrylated anthranilic aldehydes **1a–d** were synthesized in three steps as shown in Scheme 2. The alkylation of quinoline with alkyl iodides (1,4-dioxane, reflux) afforded the *N*-alkylquinolinium salts **5a**,**b**. Oxidation of the latter with H_2O_2 gave *N*-alkylanthranilic aldehydes **6a**,**b**.[31] Finally, products **1a–d** were obtained by reaction of **6a**,**b** with acryloyl chloride (**7a**) or (*E*)-crotonyl chloride (**7b**) according to a known methodology.[5]

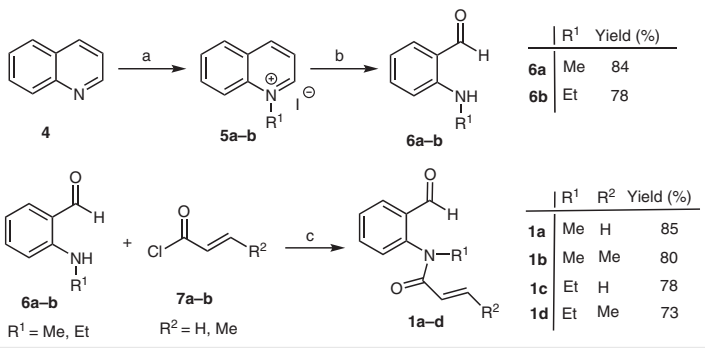
The synthesis of the desired target molecules was next studied. To optimize the conditions of the DKHDA reaction, the synthesis of product **3a** by reaction of *N*-acrylanthranilic aldehyde **1a** with *N*-phenylpyrazolone **2a** was investigated (Table 1). Initially, the effect of the solvent, such as water, acetonitrile, methanol, ethanol, acetic acid, and toluene, was studied. The reactions were carried out under reflux and catalyst-free conditions at a reaction time of 15 hours

Table 1 Optimization of the Synthesis of **3a**[a,b]

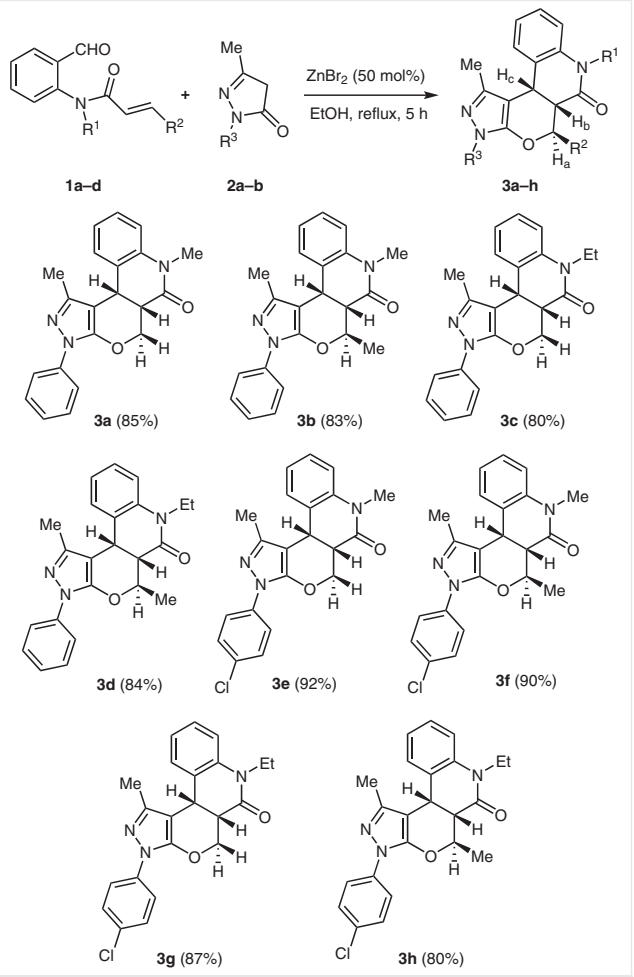


Entry	Solvent	Additive (mol%)	Temp (°C)	Yield[b](%)
1	H_2O	–	reflux[c]	13
2	MeCN	–	reflux[c]	15
3	MeOH	–	reflux[c]	30
4	EtOH	–	reflux[c]	32
5	AcOH	–	reflux[c]	5
6	$PhCH_3$	–	reflux[c]	18
7	EtOH	ZnO (100)	reflux[d]	48
8	EtOH	$ZnCl_2$ (100)	reflux[d]	67
9	EtOH	$ZnBr_2$ (100)	reflux[d]	85
10	EtOH	NEt_3 (100)	reflux[d]	10
11	EtOH	L-proline (100)	reflux[d]	20
12	H_2O	$ZnBr_2$ (100)	reflux[d]	25
13	**EtOH**	**$ZnBr_2$ (50)**	**reflux[d]**	**85**
14	EtOH	$ZnBr_2$ (40)	reflux[d]	80

[a] *Reagents and conditions*: **1a** (0.5 mmol, 1.0 equiv), **2a** (0.5 mmol, 1.0 equiv), and solvent (5.0 mL).
[b] Yields of isolated products.
[c] Reaction time: 15 h.
[d] Reaction time: 5 h.



Scheme 2 Synthesis of **1a–d**. *Reagents and conditions*: (a) R^1I, 1,4-dioxane, reflux, 1 h; (b) 1,2-dichloroethane/H_2O (1:1), KOH, H_2O_2, 72 h; (c) $NaHCO_3$, CH_2Cl_2, 2–5 h.

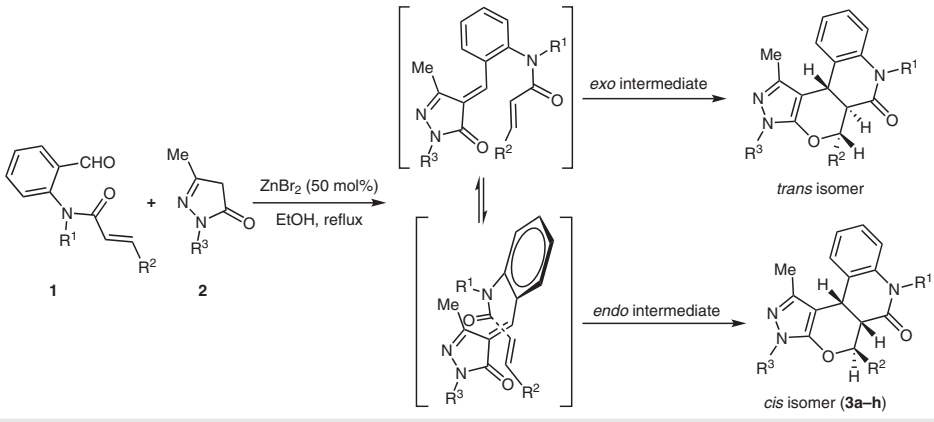


Scheme 3 Preparative scope. *Reagents and conditions*: **1** (0.5 mmol, 1.0 equiv), **2** (0.5 mmol, 1.0 equiv), $ZnBr_2$ (0.25 mmol, 0.5 equiv), and EtOH (5.0 mL), reflux, 5 h. Isolated yields are given in parenthesis.

(entries 1–6, Table 1). The best yields were obtained in ethanol (32% yield, entry 4). Subsequently, the effect of the Lewis acid, such as ZnO, $ZnCl_2$, and $ZnBr_2$, was studied. In the presence of Lewis acid, the yields were improved to 48, 67, and 85%, respectively, and the reaction time could be reduced to five hours (entries 7-9). In fact, employment of $ZnBr_2$ in ethanol heated to reflux gave the best yields (85%, entry 9). The use of other catalysts, such as the acid L-proline or the base NEt_3, was not successful (entries 10 and 11). Likewise, the use of $ZnBr_2$ in water heated to reflux was not successful (entry 12). Reduction of the amount of $ZnBr_2$ to 50 mol% gave equally good yields (85%), but further reduction of the amount of $ZnBr_2$ (40 mol%) gave lower yields (entries 13 and 14). Hence, the optimized reaction conditions involved ethanol at reflux with 50 mol% of $ZnBr_2$ and a reaction time of five hours (entry 13).[32] In all cases, analysis of the ^1H NMR spectrum of **3a** revealed that the product was selectively obtained as the *cis*-configured isomer.

By using the optimized conditions, the substrate scope was studied. The cyclization of pyrazolones **2a**,**b** with anthranilic aldehydes **1a–d** afforded products **3a–h** in 80–90% yield and with very good regio- and diastereoselectivity (Scheme 3).

The structure of the products was confirmed by spectroscopic methods. The coupling constants of the adjacent H atoms clearly indicate the *cis* configuration of the products (comparison with ^1H NMR data of related molecules reported in the literature).[1–5] For example, in the ^1H NMR spectrum of compound **3d**, a one-proton double doublet with coupling constants of 7.3 Hz and 5.2 Hz is observed for proton H_b at 2.84 ppm, a three-proton multiplet for the N-CH_2 and H_a protons at 3.88–4.03 ppm, and a one-proton doublet with a coupling constant of 5.1 Hz for proton H_c at 4.25 ppm. These data indicate that H_a and H_b are in a *trans* relationship and H_b and H_c are in a *cis* relationship (for assignment of the protons, see Scheme 3). In all compounds, similar coupling constants were observed. In the ^1H NMR



Scheme 4 Possible mechanism of the formation of compounds **3a–h**

spectrum of compound **3d**, there are also a three-proton triplet, doublet, and a singlet at 1.24, 1.49, and 2.27 ppm, respectively, which can be assigned to the three CH_3 groups.

A possible mechanism of the formation of products **3a–h** is illustrated in Scheme 4. The $ZnBr_2$-mediated Knoevenagel condensation of *N*-acrylanthranilic aldehyde **1** with pyrazolone **2** leads to the formation of an intermediate which can exist in an *exo* or *endo* orientation. The stereochemistry of the products depends on the stereochemical orientation of the dienophile in the transition state of the subsequent intramolecular hetero Diels–Alder reaction. The reaction seems to proceed selectively via the *endo* transition state, as exclusively the formation of the *cis*-configured isomers was observed. This might be explained by electronic reasons.

In conclusion, we have synthesized what are, to the best of our knowledge, the first tetrahydropyrazolo[4',3':5,6]pyrano[3,4-*c*]quinolones through DKHDA reaction of pyrazolones with *N*-acrylated anthranilic aldehydes. The reaction proceeds with excellent regio- and stereoselectivity and in high yields. The reaction was carried out in ethanol heated to reflux as a green and environmentally friendly solvent. The Lewis acid used, $ZnBr_2$, is inexpensive and commercially available.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690189.

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(32) **Synthesis of Products 3a–h by DKHDA Reaction; General Procedure**

A mixture of *N*-acrylated anthranilaldehyde **1** (0.5 mmol), *N*-phenyl pyrazolone **2** (0.5 mmol), and $ZnBr_2$ (50 mol%) was stirred in EtOH heated to reflux (5 mL). The progress of the reaction was followed by TLC. After completion (5 h) and cooling down, ice-cold water (20 mL) was poured into the reaction mixture. The resulting precipitate was filtered after stirring for 5 min and washed with cold water. After air drying at room temperature, the pure product **3** was obtained by column chromatography on silica gel, by eluting with *n*-hexane/ethyl acetate (2:1).

(5*R,5*aS**,11*bS**)-7-Ethyl-1,5-dimethyl-3-phenyl-5,5*a*,7,11*b*-tetrahydropyrazolo[4',3':5,6]pyrano[3,4-*c*]quinolin-6(3*H*)-one (3d)**

Pale yellow solid; yield: 84% (157 mg); mp 180–182 °C. IR (ATR): 3066, 2930, 1664, 1599, 1496, 1126, 757 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 6.4 Hz, 3 H, CH_3), 1.49 (d, *J* = 6.5 Hz, 3 H, CH_3), 2.17 (s, 3 H, CH_3), 2.84 (dd, *J* = 7.3, 5.2 Hz, 1 H, H_b), 3.88–4.03 (m, 3 H, H_a, NCH_2), 4.25 (d, *J* = 5.1 Hz, 1 H, H_c), 7.02–7.21 (m, 3 H, Ar-H), 7.27–7.40 (m, 4 H, Ar-H), 7.73 (d, *J* = 8.51 Hz, 2 H, Ar-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.7 (CH_3), 13.4 (CH_3), 18.8 (CH_3), 31.0 (CH), 38.0 (NCH_2), 46.3 (CH), 72.4 (OCH), 115.0 (CH), 120.3 (CH), 121.1 (C), 123.3 (CH), 125.6 (CH), 128.3 (CH), 128.9 (CH), 129.1 (CH), 129.8 (C), 137.4 (C), 138.5 (C), 146.8 (C), 149.4 (C), 167.2 (CON). HRMS (EI): *m*/*z* calcd for $C_{23}H_{23}N_3O_2$ $[M]^+$: 373.1785; found: 373.1781.