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Preparation of 2,4,5-trisubstituted pyrazolo[4,3-*c*]quinolin-3-ones

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ABSTRACT

The preparation of pyrazolo[4,3-*c*]quinolinones is reported starting from 2-substituted-5-(2-fluorophenyl)-3-oxo-2,4-dihydro-3*H*-pyrazol-3-ones. A one-pot protocol was developed, in which condensation with an orthoamide, followed by substitution with a primary amine and subsequent S_NAr-cyclization, to provide rapid access to 4- and 5-substituted pyrazolo[4,3-*c*]quinolinones.

During the course of an ongoing drug discovery project, access to 2,5-disubstituted pyrazolo[4,3-*c*]quinolinones (**1**, Fig. 1), a heterocyclic motif that has shown activity across a range of medicinally relevant targets (e.g., benzodiazepine receptors,[1–3] PDE 4,[4] and antiviral[5]), was required. Previously reported synthetic tactics toward the construction of 2,5-disubstituted pyrazolo[4,3-*c*]quinolinones have relied upon substituted 4-oxo-1,4-dihydroquinoline-3-carboxylate esters (**4**) as starting materials, which can be prepared via a Gould–Jacobs cyclization[6] strategy in which anilines (**2**) are reacted with ethoxyethylenemalonates (**3**). Functionality has been introduced sequentially at the 2- and 5-positions via conversion to the chloroquinoline **5**,[7] formation of the tricycle **6** and finally *N*5-alkylation.[1] Alternatively, 2,5-disubstituted pyrazolo[4,3-*c*]quinolinones can be constructed by first alkylation at *N*5, followed by formation of the *C*9b–*N*1 bond via the activated 4-thioketone quinoline ester.[4]

While these tactics are synthetically robust, they both face several limitations, including the following: (a) both *N*5- and *N*1-alkylated compounds (i.e., **6**→**1**) have been observed employing the former method;[8] (b) both methods rely upon substituted 4-oxo-1,4-dihydroquinoline-3-carboxylate esters as key building blocks, dramatically limiting the pool of potential starting materials; and (c) introduction of R^3 requires an S_N2-type alkylation, which is limited by the compatibility of the halide to undergo an S_N2-type process, precluding sterically congested substituents (i.e., *tert*-butyl) and electrophiles incompatible with the reaction conditions (i.e., sp^2-like aryl groups).

Herein we report an alternative strategy that addresses the aforementioned limitations, in which substituted 3-(2-fluorophenyl)-3-oxopropanoate esters (**7**, Fig. 2) serve as the key building block for the construction of 2,5-disubstituted pyrazolo[4,3-*c*]quinolinones in a three step sequence. Derivatives of **7**, which can be readily prepared from benzoyl chlorides,[9] were treated with

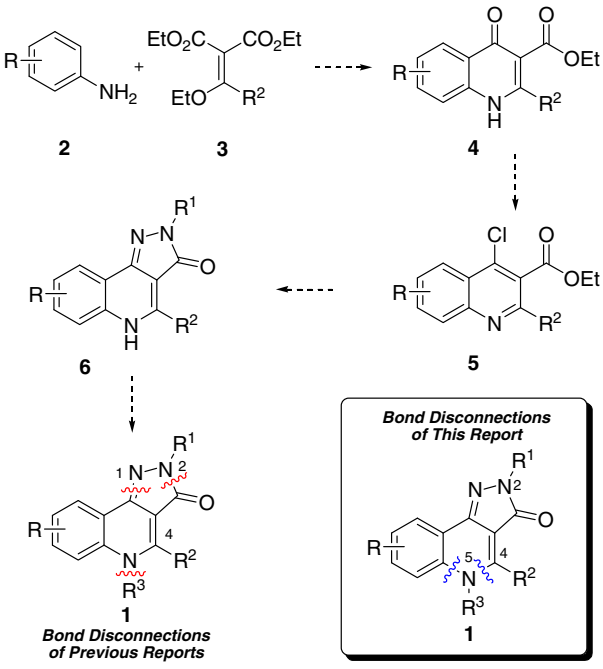

Figure 1. Strategies employed for the construction of 2,5-disubstituted pyrazolo-[4,3-*c*]quinolinones.

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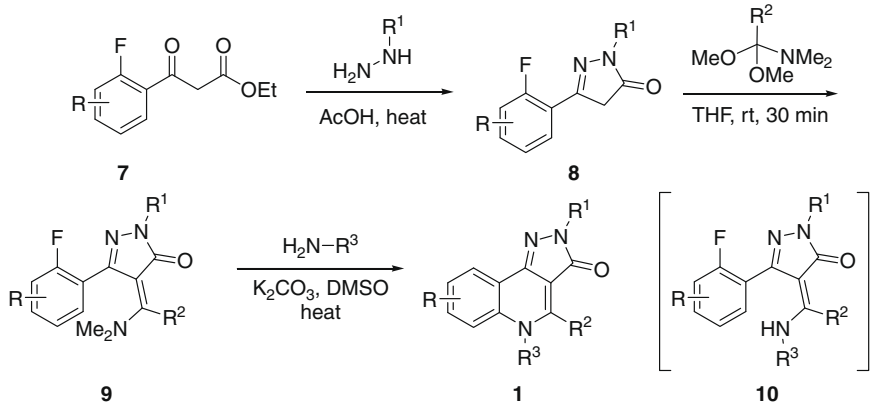
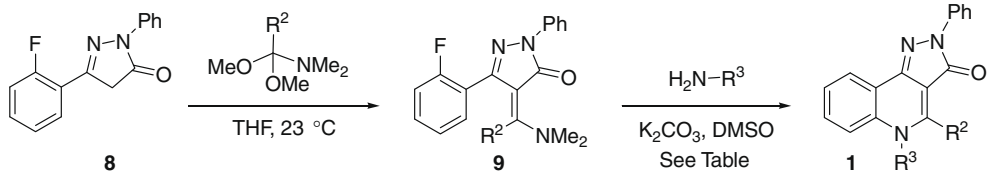


Figure 2. Three-step strategy employed for the construction of 2,5-disubstituted pyrazolo[4,3-*c*]quinolinones.

substituted hydrazines in warm acetic acid to provide 5-(2-fluorophenyl)-2,4-dihydro-3*H*-pyrazol-3-ones **8** in good to excellent yields.[10] Treatment of pyrazolone **8** with an orthoamide (R^2 = H or Me)[11] for 30 min at ambient temperature affords smooth conversion to the dimethylenamine **9**, which was used without purification. Construction of the pyrazolo[4,3-*c*]quinolinone **1** was then completed by treatment of enamine **9** with substituted primary amines in the presence of potassium carbonate in dimethylsulfoxide (Tables 1 and 2). The initial substitution reaction was facile at ambient temperature, affording the intermediate enamine **10**. The subsequent S_NAr-cyclization was then accomplished by heating the reaction mixture at elevated temperatures.

To explore the scope of the reaction, various amines were examined with substrate **9** (R = H, R^1 = Ph, Table 1). Aliphatic amines

Table 1
Amines and orthoamides evaluated in the formation of 4- and 5-substituted pyrazolo[4,3-*c*]quinolinones **1a–j**



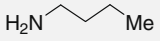
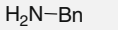
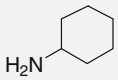
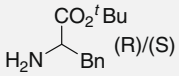
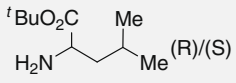
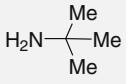
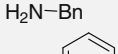
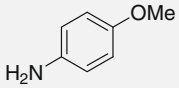
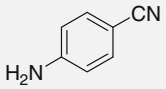
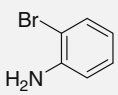
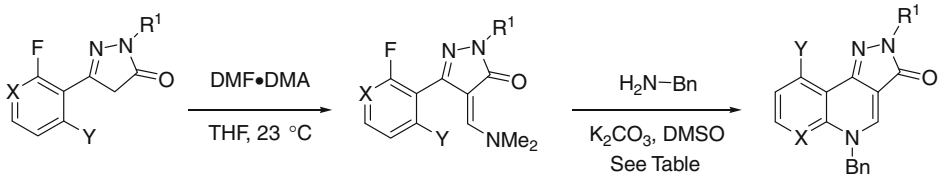
Entry	R^2	$H_2N–R^3$	Time (min)	Temp (°C)	Product	Yield (%)
1	H		30	100	**1a**	94
2	H		60	100	**1b**	92
3	H		120	100	**1c**	92
4	H		180 30	100 130	**1d**	73 65
5	H		60 30	100 130	**1e**	90 77
6	H		180 60	130 150	**1f**	48 77
7	Me		15	100	**1g**	62
8	H		45 30	130 150	**1h**	69 73
9	H		150 30	130 150	**1i**	25 52
10	H		120	130	**1j**	11
11	H		90	150	**1k**	53

Table 2
Effect of substitution at *N*2, *C*6, and *C*9 on the formation of substituted pyrazolo[4,3-*c*]quinolinones **1k–n**



8 **9** **1**

Entry	X	Y	R^1	Time (min)	Temp (°C)	Product	Yield (%)
1	CH	H		90	100	**1m**	66
2	N	H	Ph	60	23	**1n**	77
3	CH	OMe	Ph	90	100	**1p**	37

(entries 1–5) afforded pyrazolo[4,3-*c*]quinolinones **1** in moderate to excellent yields. With an increase in steric demand at the α-carbon of the amine, a corresponding increase in reaction time was required (cf. entries 1–4). In an effort to shorten the reaction time, the reaction temperature was increased from 100 °C to 130 °C (entry 4), affording similar yields. Enantiopure amino acid esters (>98% ee) were competent in the reaction as substrates (entries 4 and 5). However, complete racemization was observed for **1d** and **1e** at both 100 °C and 130 °C, which may be due to enhanced methine acidity of the resulting pyrazolo[4,3-*c*]quinolinone products. When employing *tert*-butylamine (entry 6) as a substrate, cyclization of **10** was not observed at 100 °C and required heating the mixture to higher temperature (130 °C) for the S_NAr-cyclization to proceed, providing **1f** in fair yield. By further increasing the temperature to 150 °C, the desired pyrazolo[4,3-*c*]quinolinone was obtained in shorter reaction time (60 min) and higher isolated yield (77%).[12] This sequence was also amenable to substitution of the orthoamide, as *N,N*-dimethylacetamide dimethylacetal (entry 7) was competent in this sequence, providing the corresponding 4-methylpyrazolo[4,3-*c*]quinolinone in shorter reaction time (cf. entries 7 and 2), albeit in somewhat decreased yield.

Aromatic amines were also examined (entries 8–11), affording pyrazolo[4,3-*c*]quinolinones, and yields were dependent on the steric and electronic nature of the aniline. As was observed for sterically encumbered aliphatic amines, S_NAr-cyclization of the putative intermediate **10** was not observed for aromatic amines at 100 °C. Rather, cyclization was only observed at temperatures ⩾130 °C. In addition, shorter reaction times at higher temperatures provided pyrazolo[4,3-*c*]quinolinones in higher isolated yields, as was observed in entry 6. Notably, both electron-rich and electron-deficient aromatic amines (entries 9 and 10) required longer reaction times than aniline (entry 8) and afforded product in lower yields, 52% and 11%, respectively. The sterically encumbered 2-bromoaniline (entry 11) also provided the corresponding 4-methylpyrazolo[4,3-*c*]quinolinone after 90 min at 150 °C in good yield.

The effect of substitution at *N*2, *C*6, and *C*9 was also evaluated (Table 2). Introduction of an aliphatic *tert*-butyl group at *N*2 (entry 1), afforded the pyrazolo[4,3-*c*]quinolinone **1m** in good yield with a slightly decreased yield and increased reaction time, presumably a result of increased electron density in the pyrazolone ring (cf. Table 1, entry 2). Introduction of a nitrogen atom was well-tolerated at the 6-position (entry 2), providing the desired pyrazolo[4,3-*c*]-1,8-naphthyridin-3-one **1n** in good yield after 60 min at ambient temperature. The decrease in required temperature is presumably due to the stabilizing nature of the adjacent nitrogen during the formation of the high energy Meisenheimer complex.[13] The electron donating methoxy group was tolerated at *C*9 (entry 3), providing **1p** in moderate yields.

In summary, an alternative strategy for the construction of 2,5-disubstituted pyrazolo[4,3-*c*]quinolinones has been developed. (2-Fluorophenyl)-3-oxo-2,4-dihydro-3*H*-pyrazol-3-ones (**8**) were prepared from 3-(2-fluorophenyl)-3-oxopropanoates esters (**7**) and served as a key building block. A protocol was developed in which facile condensation with an orthoamide, followed by substitution with a primary amine and subsequent S_NAr-cyclization, provide rapid access to 4- and 5-substituted pyrazolo[4,3-*c*]quinolinones.

Representative procedure: 2-Phenyl-5-(phenylmethyl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (**1a**): 5-(2-Fluorophenyl)-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (200 mg, 0.787 mmol) was dissolved in tetrahydrofuran (3 mL) and treated with *N,N*-dimethylformamide dimethylacetal (0.126 mL, 0.944 mmol, 1.2 equiv). After stirring for 30 min at ambient temperature, the mixture was concentrated in vacuo. The resulting 4-[(dimethylamino)-methylidene]-5-(2-fluorophenyl)-2-phenyl-2,4-dihydro-3*H*-pyrazolo-3-one residue was dissolved in dimethylsulfoxide (3 mL), treated with benzylamine (0.129 mL, 1.18 mmol, 1.5 equiv) and potassium carbonate (326 mg, 2.36 mmol, 3 equiv) and then stirred at ambient temperature for 30 min. The mixture was placed into a preheated oil bath at 100 °C for 1 h, cooled to ambient temperature, poured into water (50 mL) and extracted with ethyl acetate containing 5% methanol (3 × 150 mL). The combined organic extracts were dried with sodium sulfate, filtered and concentrated in vacuo. The residue was treated with ethyl acetate (20 mL) and hexanes (75 mL), aged for 30 min and then filtered. The solid was collected and dried in vacuo, providing the titled compound as a bright yellow solid (256 mg, 93% yield): IR (thin film, neat): 3032 (w), 1638 (s), 1614 (m), 1592 (m), 1488 (m), 1460 (m), 1397 (m), 1371 (m), 1325 (m), 1308 (m), 1233 (m), 1184 (w), 1165 (w), 1126 (m), 1054 (w), 1027 (w), 970 (m), 984 (w), 855 (w), 816 (w), 719 (s), 653 (m), 536 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 9.14 (1H, s), 8.30 (1H, d, J = 6.6 Hz), 8.21 (2H, d, J = 8.6 Hz), 7.76 (1H, d, J = 8.7 Hz), 7.64–7.61 (1H, m), 7.56 (1H, t, J = 7.4 Hz), 7.46 (2H, t, J = 8.0 Hz), 7.38–7.35 (2H, m), 7.34–7.28 (3H, m), 7.20 (1H, t, J = 7.5 Hz), 5.76 (2H, s) ppm; high resolution mass spectrometry (ES+) m/z 352.1444 [$(M+H)^+$; calcd $C_{23}H_{18}N_3O$: 352.1444].

Acknowledgments

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