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An alternative approach toward 2-aryl-2*H*-pyrazolo[4,3-*c*]-quinolin-3-ones by a multistep synthesis

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Dedicated to Professor Gloria I. Yranzo

ABSTRACT

A series of 2-aryl-2*H*-pyrazolo[4,3-*c*]quinolin-3-ones derivatives **6** and **7** was conveniently prepared. A multistep synthesis was carried out starting from dichloro- and bromoanilines (**1a–b**) and diethyl 2-(ethoxymethylene)malonate using a slightly modified Gould-Jacobs reaction. In this work we present a novel chlorination strategy to prepare quinoline derivatives **4** in excellent yields as key intermediates in the synthesis of the target compounds. Several reaction conditions were evaluated to optimize the formation of pyrazoloquinolinone nucleus. Differences in chemical behavior of both chloroquinolinones **4a–b** with aryl and benzyl-hydrazines are also discussed.

Benzodiazepines (BDZs) are the drugs of choice in the pharmacotherapy of anxiety and related emotional disorders. These compounds act via the benzodiazepine receptor site (BzR) on the γ-aminobutyric acid receptor complex ($GABA_A$). The central receptors located in the neuronal tissues are functionally linked to a $GABA_A$ receptor chloride ionophore complex and are apparently located in the synaptic membranes. Central BDZ receptors mediate classical pharmacological properties of the widely used benzodiazepines.[1] Ligands interacting with BzR have intrinsic activity ranging from agonists (anxiolytic, hypnotic, and anticonvulsant agents), through antagonists (without efficacy), to inverse agonists (proconvulsant and anxiogenic agents).[2] BzR includes not only substances with a benzodiazepine structure but also those chemically diverging, and they mediate a broad variety of pharmacological actions.[3] Since the discovery of chlordiaxepoxide and diazepam,[4] 1,4-benzodiazepines have been an important source of research. However, these anxioselective compounds have shown undesirable side effects and the design and development of truly innovative drugs are further required. Thus, the study of 2-aryl-2,5-dihydropyrazolo[4,3-*c*]quinoline-3-ones as high affinity BzR ligands has been an interesting contribution to the development of new bioactive compounds.[5] The absence of adverse effects found in benzodiazepine structures and the wide spectrum of the biological activity observed contribute to constituting pyrazoloquinolinone nucleus as an important structural target. We studied the synthesis of this type of compounds on the basis of the rationalization of the common structural requirements for binding to BzR (Fig. 1).[6]

The multistep synthesis described here involves classical,[7,8] novel, and alternative steps. The optimization of the whole methodology allowed us to afford different compounds in each step in good to very good yields.

We also discuss the effect of the reaction conditions in the last path to prepare both benzyl-pyrazoloquinolinones derivatives: 2-benzyl-7,9-dichloro-2*H*-pyrazolo[4,3-*c*]quinolin-3-one (**6d**) and 2-benzyl-8-bromo-2*H*-pyrazolo[4,3-*c*]quinolin-3-one (**7d**). Here, 1-benzyl-isomer products (**6e** and **7e**) were also obtained and the regioselectivity of the reaction depends on the nature of the starting quinolinone.

All pyrazoloquinolinones were prepared through the synthesis outlined in Scheme 1.

Diethyl 2-((phenylamino)methylene)malonates **2a**,**b** were prepared by the nucleophilic reaction of aromatic amines **1a**,**b** and diethyl 2-(ethoxymethylene)malonate by a Gould–Jacobs cyclization according to the procedure in the literature.[9] Without purification, malonates **2a**,**b** were thermally cyclized in diphenylether (DPE)[10,11] to give ethyl-4-oxo-1,4-dihydroquinoline-3-carboxylates **3a**,**b**. Several attempts were made to optimize this reaction. Reflux in DPE (at 257 °C) led to the decomposition of the solvent and to a high contamination of the final products. Using the same solvent at

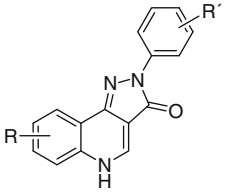

Figure 1. General structure of 2-aryl-2*H*-pyrazolo[4,3-*c*]quinolin-3-ones derivatives.

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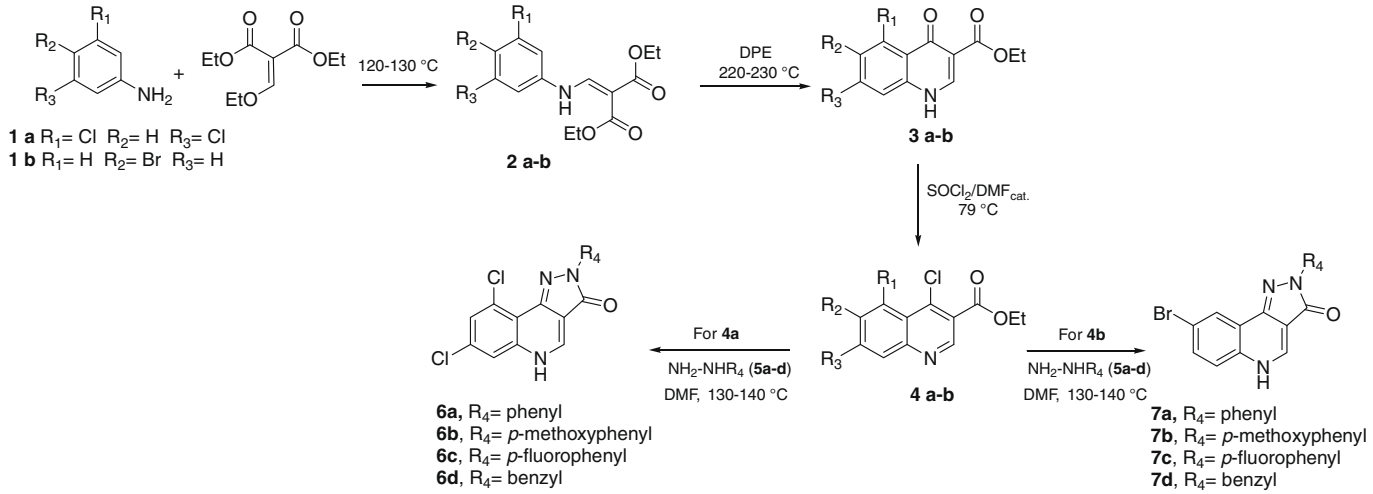


Scheme 1. Multistep synthesis of pyrazoloquinolinones **6a–d** and **7a–d**.

180–210 °C, the reaction was cleaner but the yields were too low (25–30%). At 220–230 °C, and with strict control of the temperature, compounds **3a** and **3b** were prepared in good yields, 78% and 71%, respectively, calculated from aniline precursor. Compound **3a** was not reported in the literature whereas **3b** was prepared from diethyl-4-bromoanilinomethylenemalonate (**2b**) in 57% yield[12] showing that our procedure was found to be more efficient.

Dihydroquinoline-3-carboxylates were inert to react with hydrazines to give the expected pyrazoloquinolinones **6** and **7**. For this reason the halogenation of quinolines was achieved to prepare chloroderivatives which could react with nucleophilic hydrazines. Numerous attempts were made to obtain compounds **4**. First, the reported halogenation treatments using an excess of $POCl_3$ (0.04 mol of **3a** and 0.27 mol of $POCl_3$)[8a] at reflux temperature did not lead to the corresponding 4-chloroquinoline, and the starting quinolinone was recovered. When **3a** was treated with PCl_5 (10% of mol of **3a**) and $POCl_3$ (excess) in a range of temperature from 0 to 25 °C,[13] a mixture of products was obtained without the quantitative formation of the compound **4a**. NMR analysis of the crude showed that, in addition to product **4a**, a quinoline-3-carboxilic acid derivative was formed. The formation of this acid could result from the hydrolysis of a quinoline-3-carbonyl chloride obtained as intermediate in the halogenation process.

One of the possible difficulties to obtain chloroderivatives **4** was the tendency of these compounds to undergo hydrolysis and re-establish the starting quinolinone. Having this in mind, the reaction was then carried out in $SOCl_2$ (excess) at reflux temperature with catalytic amount of DMF. After 1.5 h the crude was exhaustively evaporated without additional workup. We were pleased to discover that the solid thus prepared ($\geqslant$98% yield) was chloroquinoline **4a** in excellent conditions to be used in the next step.

This protocol was adopted in the chlorination of quinoxalinediones,[14] however, there are no precedents of their utilization in the chlorination of quinolinones. We examined this methodology for the preparation of **4b**. In this case, the reaction yielded a quantitative conversion (100% yield) within 2 h. In our reactions, it was observed that the use of DMF was not mandatory and analogous excellent yields were obtained in the absence of this catalyst.

Optimization of the chlorination step was crucial for the successful development of this synthetic methodology since the chloroderivatives thus prepared were stable enough to allow the reaction with different hydrazines.

Chloroquinolines **4a**,**b** were cyclized with aryl (**5a**–**c**)- and benzyl (**5d**)-hydrazines to afford pyrazoloquinolinones **6a–d** and **7a–d**, respectively (Table 1).[15] The reaction consisting of a nucleophilic substitution of the chlorine atom by the hydrazine derivative followed by cyclization[10] confirmed once again its usefulness for the goal proposed. In all reactions, anhydrous DMF was used as solvent and cyclizations were complete over 1-2 h at 130–140 °C. In the case of cyclizations with hydrazine monohydrochloride (**5b**,**c**) and benzylhydrazine dihydrochloride (**5d**), a previous neutralization with sodium methoxide solution (12.5% w/v) was needed.

Table 1
Yields of pyrazoloquinolinones **6** and **7**

Compound	R_1	R_2	R_3	R_4	Yield[a]
6a	Cl	H	Cl	Phenyl	71[b]
6b	Cl	H	Cl	*p*-Methoxyphenyl	40[c]
6c	Cl	H	Cl	*p*-Fluorophenyl	40[c]
6d	Cl	H	Cl	Benzyl	15[c]
7a	H	Br	H	Phenyl	53[b]
7b	H	Br	H	*p*-Methoxyphenyl	35[c]
7c	H	Br	H	*p*-Fluororophenyl	50[c]
7d	H	Br	H	Benzyl	10[d]
7e	H	Br	H	Benzyl	9[d]

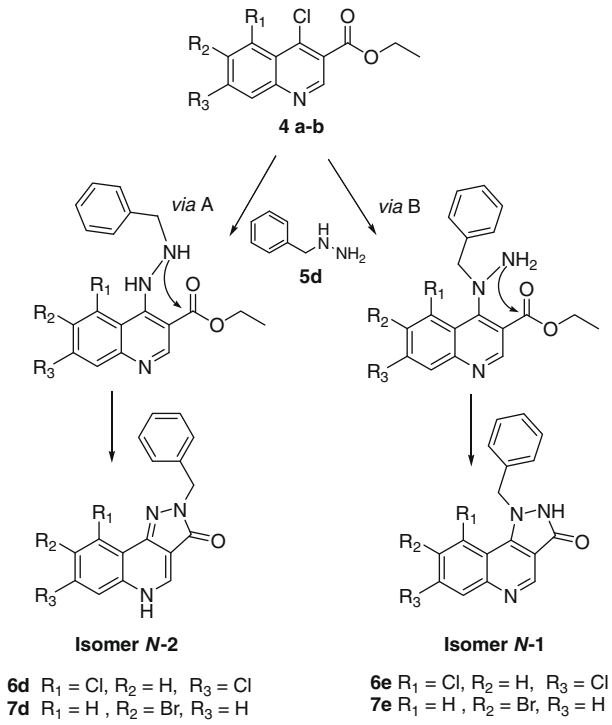
[a] Isolated product.
[b] Reactions with free phenylhydrazine.
[c] Reactions with hydrazine monohydrochloride.
[d] Reactions with hydrazine dihydrochloride.

All pyrazoloquinolinones were isolated in good to very good yields (35–71%), except in the case of benzylderivatives where the yields did not overcome 15%. To the best of our knowledge, all compounds are new except **6a**.[15]

To test the effect of hydrochloride salt or hydrazine-free nucleophiles in the yield of the reaction, pyrazoloquinolinone **7a** was synthesized from phenylhydrazine and phenylhydrazine monohydrochloride. It was surprising to find that better yield (62%) was achieved when monohydrochloride salt was used, probably due to stabilization of hydrazine as nucleophilic species.

When the cyclization reaction of chloroquinolines **4a**,**b** was performed using benzylhydrazine dihydrochloride and 2 equiv of methoxide (NaOMe) as base, one isomer (*N*-1) of these structures, derivatives **6e** and **7e**, was obtained in addition to the awaited products (**6d** and **7d**) (Scheme 2). For a thorough characterization of isomers *N*-1 and *N*-2, a careful isolation of compounds **6d**, **7d,** and **7e** was achieved. Although many attempts were made to afford isolated **6e**, it was not obtained and such compound was identified from a mixture with **6d**.

^{1}H NMR experiments showed similar signals for isomers **7d** and **7e**. ^{13}C NMR analysis of both compounds showed a significant dif-



Scheme 2. Formation of pyrazoloquinolinones isomers *N*-1 and *N*-2.

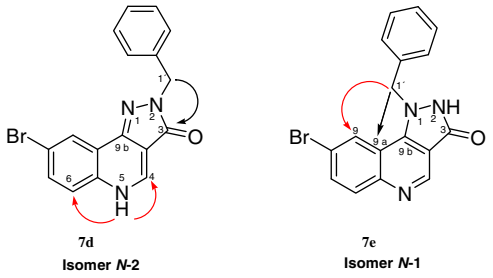


Figure 2. Diagnostic HMBC (black arrow) and ROESY (red arrow) correlations for compounds **7d** and **7e**.

ference in the shifts of signal due to carbon at position 9b (*C*-9b) (Fig. 2). In the case of **7d**, the signal appeared at 140.5 ppm, a typical shift found for iminic carbons, while a vinylic signal at 117.5 ppm was found for the same *C*-9b in compound **7e**. A complete elucidation of the structures was achieved by spectroscopic techniques of 1D NMR ROESY and 2D NMR HMBC and HSQC (Fig. 2). Thus, in the ROESY experiment, two significant signals (5.86 ppm and 8.53 ppm) corresponding to the interaction between methylene protons (*H*-1′) and proton *H*-9 were found for isomer **7e**. This correlation indicated a spatial approach (spatial distance <2.5 Å) between both types of hydrogen. ROESY analysis of **7d** did not show a signal corresponding to this type of interaction, but a signal assigned to the interaction of amine proton with protons *H*-4 and *H*-6 was observed. HMBC analysis of compound **7d** showed correlations between methylene protons (*H*-1′) and the carbonylic carbon signal at position 3. In the case of isomer **7e**, a signal corresponding to the interaction of *H*-1′ and *C*-9 was observed. For isomer **7e**, HMBC spectra showed correlations between methylene protons 1′ and the bridge *C*-9a.

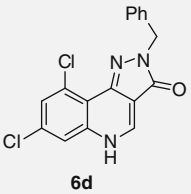
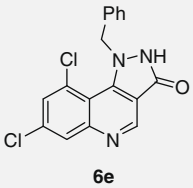
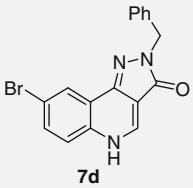
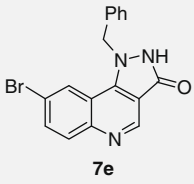
These findings allowed us to confirm the structures of pyrazoloquinolinones **7d** and **7e**.

It is evident that the presence of these isomers relates to the aliphatic nature of the hydrazine substrate since, in the case of aromatic hydrazines, only one pyrazoloquinolinone was obtained. In the reactions performed with aromatic hydrazines (**5a–c**), the primary amino group displaced the halogen following the mechanism described in, via A, Scheme 2, whereas in the reactions with benzylhydrazine, both amino groups (primary and secondary) could substitute the chlorine atom. In all experiments with quinoline **4a**, isomer **6d** was mostly found while in the cyclizations of **4b**, the ratio of isomers **7d** and **7e** showed variations (Table 2). Thus, in the case of dichloride derivative **4a**, the relationship of **6d**:**6e** was equal to 82:18, whereas in the case of the bromide derivative **4b** the relationship of **7d**:**7e** equaled 47:53.

The small amount of isomer **6e** in the reaction mixture could be rationalized if we analyzed the structure of the starting material **4a**. In this case the halogenated substituent at position 9 could inhibit the nucleophilic substitution by the *N*-2 of the hydrazine to form the pyrazolone ring (via *B*). Therefore, the initial displacement of chlorine by the primary amino group of hydrazine followed by cyclization (via *A*) seems more favorable. When R_1 = H (**4b**), the two types of cyclization are equally possible.

Encouraged by this result, we decided to study different conditions so as to form pyrazoloquinolinone isomers. Thus, when 1 equiv of sodium methoxide was used in the neutralization of benzylhydrazine dihydrochloride, the relationship of isomers **6d**:**6e** remained unaltered (81:19) and the relation of the isomers **7d**:**7e** amounted to 31:69. The steric impediment of substrate **4a** to form isomer **6e** was also demonstrated. The increase in the

Table 2
Relative ratio of isomers *N*-1 and *N*-2 determined by ^{1}H NMR

Substrate	Base, equivalents	Time (h)	 6d	 6e	 7d	 7e
4a	NaOMe[a], 2	1.5	82	18	–	–
	NaOMe[a], 1	1.5	81	19	–	–
	TEA[b], 2	4	87	13	–	–
	TEA[b], 1	4	68	32	–	–
4b	NaOMe[a], 2	1.5	–	–	43	57
	NaOMe[a], 1	1.5	–	–	31	69
	TEA[b], 2	4	–	–	28	72
	TEA[b], 1	4	–	–	–	100

[a] Solution 12.5% w/v.
[b] Anhydrous triethylamine.

amount of isomer **7e** may result from the first deprotonation of secondary amine and the favored displacement of halogen from the *N*-2 nucleophilic centre. When triethylamine (TEA) was used as base, the relative ratio of isomers for each pyrazoloquinolinone was modified. Thus, in the case of the reaction of **4a**, by using 2 equiv of TEA, the formation of isomer **6d** in the amount similar to that of the reactions with sodium methoxide was favored. When only 1 equiv of base was employed, the proportion of isomer **6e** increased due to a better deprotonation of *N*-2 in the hydrochloride salt. In the reactions of substrate **4b**, the effect of TEA as base was particularly noticeable. Thus, by using 1 equiv of base, isomer **7d** was not detected, and the reaction gave rise selectively and exclusively to regioisomeric pyrazoloquinolinone **7e**. It should be noted that the reactions with TEA were completed in 4 h, whereas the transformations with NaOMe were completed in 1.5 h.

These results show that the regiochemistry of the reaction depends on the nature of the base reagent and on the amount employed in the neutralization of the starting hydrazine. A similar behavior was found in the reaction of 3-acyl-4-methoxy-quinolinones with *N*-substituted hydrazines to prepare 2,5-dihydro-4*H*-pyrazolo[4,3-*c*]quinolinones.[16] Here the regioselectiviy of the reaction changes markedly if free hydrazine or hydrazine hydrochloride is used as a base. On the other hand, a regioselective behavior was analyzed in the synthesis of pyrazolo[4,3-*c*]pyrrolo[3,2-*f*]quinolin-3-one derivatives where the use of methylhydrazine favored the *N*-1-methyl isomer and the use of arylhydrazines exclusively favored *N*-2-aryl isomers.[17,18]

In conclusion, we have prepared pyrazolo[4,3-*c*]quinolin-3-ones (**6**,**7**) in a multistep protocol from simple anilines. This novel approach involved a simple and convenient halogenation of quinolinone-3-carboxylates (**3a**,**b**) with $SOCl_2$ to obtain the key intermediate precursors (**4a**,**b**) of the target compounds. With the present methodology, the regioselectivity achieved in the last cyclization step when arylhydrazines were used is worth noting. In this case, *N*-1 isomers were obtained, whereas in the reaction with benzylhydrazines, isomers *N*-1 and *N*-2 were synthesized.

Acknowledgments

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Supplementary data

Supplementary data (general procedures, additional experimental descriptions, NMR, HMRS and MS analysis of all products are presented) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.123.

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15. *Representative procedure to prepare 7,9-dichloro-2-phenyl-2H-pyrazolo[4,3-c]quinolin-3(5H)-one* (**6a**): Aniline **1a** (3 mmol) and diethyl(ethoxymethylene)-malonate (3 mmol) were mixed and heated at 120–130 °C for 5.5 h to give malonate **2a**. This compound was treated with diphenylether (DPE, 10 mL) at 220–230 °C for 4 h to afford quinolone **3a** (78% yield). Then, **3a** (0.8 mmol) was mixed with thionyl chloride (0.5 mL) and a drop of DMF at reflux temperature for 1 h to give chloroquinolines **4a**. Thionyl chloride excess was removed by evaporation and co-evaporation with dichloromethane (3×10 mL). Pyrazoloquinolinones **6a** was obtained by reaction between **4a** (0.8 mmol) and phenylhydrazine **5a** (1 mmol) in DMF at 130–140 °C. This compound was obtained as a yellow solid after a column chromatographic purification process (71% yield), mp > 310 °C dec. ^{1}H NMR (400.16 MHz, [$(CD_3)_2SO$]), δ (ppm): 7.20 (t; J = 7.3 Hz; 1H); 7.46 (t; J = 7.6 Hz and J = 8.2 Hz; 2H); 7.67 (d; J = 1.8 Hz; 1H); 7.75 (d, J = 1.8 Hz; 1H); 8.21 (d; J = 8.3 Hz; 2H); 8.77 (*s*; 1H); 12.1 (*s*; 1H). ^{13}C (100.04 MHz, TFA), δ (ppm): 107.7; 116.0; 117.6; 118.6; 124.3; 127.3; 128.7; 131.4; 133.5; 138.1; 139.7; 139.8; 141.1; 160.9. MS (EI): m/z (%) = 330 [M^+] (73), 294 (80), 300 (15), 259 (7), 223 (20), 196 (33), 161 (27), 77 (100). HMRS (ESI$^+$): calcd for $C_{16}H_{10}N_3Cl_2O$ 330.0201; found 330.0204. See the Supplementary data.
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