A One-Pot Rearrangement of 2-(*N*-Alkyl-*N*-aryl)aminochromone-3-carbaldehyde to *N*-Alkyl-3-salicyloyl-2-quinolone – An Antileishmanial Agent

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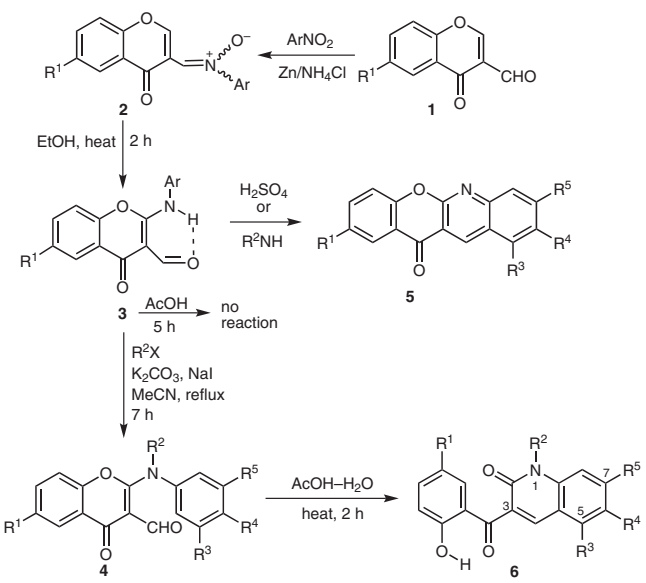
Abstract: 2-(*N*-Aryl)aminochromone-3-carbaldehyde does not show any change on heating in acetic acid, but under the same reaction conditions 2-(*N*-alkyl-*N*-aryl)aminochromone-3-carbaldehyde rearranges to 3-salicyloyl-2-quinolones, which exhibits antileishmanial activity.

Key words: 3-formylchromone, 1-benzopyran, 2-quinolone, 2-amino-3-formylchromone, molecular rearrangement, heterocycles

The 2-quinolone moiety is widely distributed in the field of natural products[1] and has found diverse applications in medicinal chemistry. 2-Quinolones having appropriate substitution at their 3-position exhibit antibacterial,[2] anti-inflamatory,[3] antithyroid,[4] and antitumor activities.[5] Recently, 4-anilino-8-methyl-6-methanesulphonyl-2-quinolone-3-carboxamide have been patented as inhibitors of phosphodiesterase.[6] 3-Aminoquinolin-2-one acts as an antiparasitic, antituberculosis, and antiangiogenic agent.[7] Atanine, a naturally occurring compound possesses antiparasitic activity.[8] 7-Amino-2-quinolones have been used as laser dyes with blue-green emission[9a] and a recent report describes that *N*-methyl-2-quinolone helps switching electrical conductivities by its photodimerization mechanism.[9b]

3-Formylchromone (**1**), beside its biological activities,[10] has proved itself to be a very good substrate for the synthesis of chromone-fused or chromone-linked heterocycles.[11] 2-Arylaminochromone-3-carbaldehyde (**3**) has been synthesized from **1** via the nitrone **2**[12] or by directly treating **1** with nitro compounds.[13] Compound **3** can be converted into a tertiary amine **4** followed by substitution with various nucleophiles.[14] Latterly, we have utilized **3** for the synthesis of bischromones involving a deformylative Mannich reaction,[15] to prepare chromeno[2,3-*b*]-pyridines with varying substituents at their 3-position.[16] 2-(*N*-allyl-*N*-aryl)aminochromone-3-carbaldehyde has also been used for intramolecular [3+2]-nitrone cycloaddition reaction at low temperature involving *N*-methylhydroxylamine,[17] while we have utilized the same compound for intramolecular [3+2]-azomethine ylide cycloaddition reaction[18] and for domino Knoevenagel–hetero Diels–Alder reaction.[19]

Different methods for the synthesis of the 2-quinolone moiety have been reported.[20] Some recent reports include the use of a pseudo-domino Heck–Buchwald–Hartwig reaction,[21] reaction of anilines with Meldrum's acid,[22] Wadsworth–Emmons olefination,[23] and trifluoroacetic anhydride induced cyclization of *N*-methyl cyanoacetanilide.[24] We report herein the synthesis of 3-salicyloyl-2-quinolones by a one-pot rearrangement of 2-(*N*-alkyl-*N*-aryl)aminochromone-3-carbaldehyde **4**.



Scheme 1

Sulfuric acid induced cyclization of **3** produced chromenoquinoline **5** (Scheme 1).[12,13] Similar cyclization was also accomplished by using secondary amines.[15] It was of interest to study how **3** would behave towards glacial acetic acid but, on heating **3** in glacial acetic acid for 5 hours, no change was observed. It was assumed that, unlike H_2SO_4, acetic acid does not protonate the carbonyl oxygen of **3**, which is engaged in hydrogen bonding with the NH at C-2. Under this hydrogen-bonded condition the phenyl group fails to achieve the correct orientation for cyclization. To verify this assumption, compound **3** was alkylated to **4** by heating **3** with alkyl halide (R^2X) in the presence of K_2CO_3 and NaI in MeCN for 7 hours

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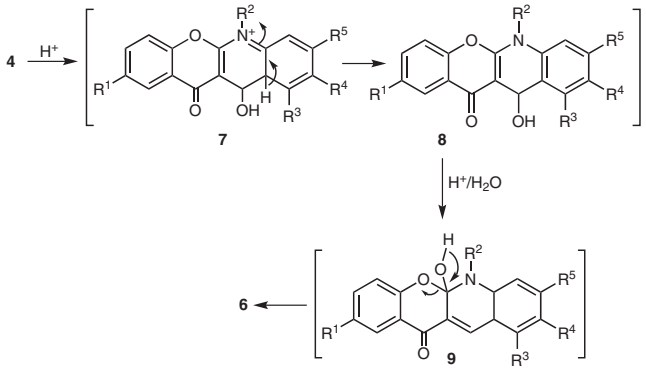
(Scheme 1). In the absence of H bonding in **4**, the possibility of the aromatic ring achieving the correct orientation for cyclization involving the formyl function of **4** increases. Indeed, on heating **4** in glacial acetic acid for 5 hours, the reaction mixture produced quinolone **6** in excellent yield (Table 1).[25] The structure of compound **6** was established on the basis of full spectroscopic analysis. Formation of **6** was rationalized by considering the acid-induced cyclization involving the phenyl ring and the formyl function of **4** to form **8** via **7** (Scheme 2). Acid-catalyzed rearrangement of **8** produces **9**, which tautomerizes to quinolone **6**. The proposed mechanism demands the presence of water in the reaction mixture. Indeed, when the above reaction was performed in glacial acetic acid containing a few drops of water, the reaction was complete within 2 hours.



Scheme 2

To estimate the strength of external acid required to protonate the intramolecular H-bonded formyl function of **3**, reactions were carried out under different acidic conditions, heating **3** in methanol in the presence of concentrated HCl, in MeOH in the presence of *p*-toluenesulfonic acid, in chloroacetic acid, in trifluoroacetic acid, in HCOOH, but none of the these attempts produced **5**.

The appropriate choice of substitution on the nitroarene, employed for the synthesis of **3** (Scheme 1) and suitable choice of alkyl halide (R^2X) provide a means of introducing suitable substituents on the phenyl ring and on nitrogen atom, respectively, of the quinolone moiety. Nitrobenzenes having varying substituents were employed for the synthesis of **3**, which on subsequent methylation (→ **4a–e**) and rearrangement by heating in acetic acid containing a few drops of water produced **6a–e** in excellent yields (Table 1, entries 1–5). Alkylation was also performed using allyl or crotyl bromide to obtain N-allylated products **4f–h**,[18,19] which, on subsequent heating in acetic acid, produced **6f–h** (entries 6–8). Functional-group tolerance was tested using ester, nitro, or methoxy substituents, and the mode of cyclization was tested using a wide range of electron-donating and electron-withdrawing groups at the *meta* position of the *N*-aryl moiety in **4**. On heating **4i** (R^3 or $R^5 = CO_2Et$) in aqueous acetic acid for 2 hours, the reaction mixture yielded a mixture of **6i** ($R^3 = CO_2Et$) and **6j** ($R^5 = CO_2Et$) in a 1:2 molar ratio, which were separated by column chromatography (entries 9, 10). The difference in product population was initially assumed to be due to steric effects but, on carrying out the rearrangement with **4k** (R^3 or R^5 = Me), a single product **6k** (R^3 = Me) was obtained (entry 11), which clearly ruled out the steric effects and so electronic factors are presumed to be responsible. Electron-donating groups at the *meta* position appear to favor 5-substituted quinolones; whereas electron-withdrawing groups favor 7-substituted quinolones. To verify this a stronger electron-withdrawing group (NO_2) was introduced into the substrate. On heating **4l** (R^3 or $R^5 = NO_2$), it produced **6l** ($R^5 = NO_2$) as the only isolated product (entry 12). Similarly, a substrate with stronger electron-donating group **4m** (R^3 or R^5 = OMe) produced only **6m** (R^3 = OMe, entry 13). Substrates having weakly *ortho*/*para*-orienting groups **4n** (R^3 or R^5 = Cl) produced a mixture of **6n** (R^3 = Cl) and **6o** (R^5 = Cl) with the latter predominating (entries 14 and 15).

Table 1 Synthesis of **6** by the Rearrangement of **4** Having Various Substituents

Entry	R^1	R^2	R^3	R^4	R^5	Compd	Mp (°C)	Yield (%)	Compd	Mp (°C)	Yield (%)
1	H	Me	H	H	H	**4a**	188–190	87	**6a**	182–184	86
2	Me	Me	H	H	H	**4b**	188–190	85	**6b**	222–224	85
3	Me	Me	H	Me	H	**4c**	162–164	86	**6c**	224–226	88
4	H	Me	H	Me	H	**4d**	164–166	85	**6d**	190–192	90
5	H	Me	H	Cl	H	**4e**	182–184	81	**6e**	216–217	93
6	Me	Allyl	H	H	H	**4f**	162–164	75	**6f**	136–138	80
7	Me	Crotyl	H	H	H	**4g**	136–138	82	**6g**	158–160	70
8	Me	Allyl	H	Me	H	**4h**	164–166	80	**6h**	160–162	95
9	H	Me	E[a]	H	H	**4i**	184–186	84	**6i**	174–176	30
10	H	Me	H	H	E[a]	**4i**	184–186	84	**6j**	246–248	60

Table 1 Synthesis of **6** by the Rearrangement of **4** Having Various Substituents (continued)

Entry	R^1	R^2	R^3	R^4	R^5	Compd	Mp (°C)	Yield (%)	Compd	Mp (°C)	Yield (%)
11	H	Me	Me	H	H	**4k**	108–110	65	**6k**	184–186	85
12	H	Me	H	H	NO_2	**4l**	192–194	45	**6l**	194–196	65
13	H	Me	OMe	H	H	**4m**	153–154	82	**6m**	202–203	80
14	H	Me	Cl	H	H	**4n**	155–156	75	**6n**	157–158	35
15	H	Me	H	H	Cl	**4n**	155–156	75	**6o**	218–219	50

[a] E = CO_2Me.

A preliminary investigation on the antiproliferative effect of 2-quinolones (**6**) on *L. donovani* promastigotes were carried out. *L. donovani* promastigotes were incubated with miltefosine[26] (a promising drug under clinical trial) and graded concentrations of quinolone derivatives **6** (2 μg/mL; 5 μg/mL and 10 μg/mL) and the antiproliferative effect was determined at three different time points (2 d, 4 d, and 6 d). Of the different compounds tested, compound **6a**, **6h** and **6k** were found to inhibit the growth in a dose dependent manner (Figure 1). At high doses of10.0 μg/mL, **6h** and **6k** were highly effective and inhibited by approximately 91.64% (P <0.01 vs. DMSO control) and 78.36% (P <0.02 vs. DMSO control), respectively, on the fourth day of culture. Highest activity was found on the sixth day using 10.0 μg/mL of **6h** and **6k** (inhibited by 96.00% and 87.77%, respectively) and statistically significant (P <0.003 vs. DMSO control for each experiment). A detailed investigation on the antileishmanial activity of **6** is in progress.

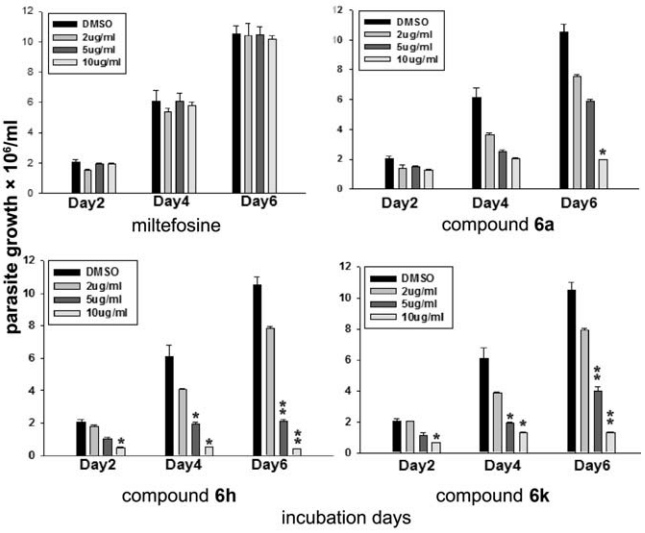


Figure 1 Data shown are the representative of three similar experiments. The error bars represent means ± SD. $^{*}P$< 0.03 vs. DMSO control; $^{**}P$ <0.009 vs. DMSO control

In summary, we have revealed a synthesis of the 2-quinolone system from aromatic nitro compounds using 3-formylchromone as a three-carbon donor. Studies of the effect of substituents on the nitroarene showed that electron-withdrawing groups (CO_2Me, NO_2) at the *meta* position favored the formation of 7-substituted-2-quinolones, whereas electron-donating groups (Me, OMe) at the *meta* position yielded 5-substituted-2-quinolones as the preferred product. Some of the synthesized quinolones exhibit significant antileishmanial activity.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) (a) Khalid, S. A.; Waterman, P. G. *J. Nat. Prod.* **1982**, *45*, 343. (b) Sarker, S. D.; Waterman, P. G.; Armstrong, J. A. *J. Nat. Prod.* **1995**, *58*, 574.
(2) Sorgel, F.; Mahr, G.; Granneman, G. R.; Stephan, U.; Nickel, P.; Muth, P. *Clin. Pharmacokinet.* **1992**, *22*, 165.
(3) Ukrainets, I. V.; Taran, S. G.; Evtifeeva, O. A.; Turov, A. V. *Chem. Heterocycl. Compd.* **1993**, *29*, 938.
(4) Ukrainets, I. V.; Taran, S. G.; Bezuglyi, P. A.; Kovalenko, S. N.; Turov, A. V.; Marusenko, N. A. *Chem. Heterocycl. Compd.* **1993**, *29*, 1044.
(5) Joseph, B.; Darro, F.; Behard, A.; Lesur, B.; Collignon, F.; Decaestecker, C.; Frydman, A.; Guillaumet, G.; Kiss, R. *J. Med. Chem.* **2002**, *45*, 2543.
(6) Jones, A.; Shipley, T. J. WO 2006/089689, **2006**.
(7) Muscia, G. C.; Bollini, M.; Bruno, A. M.; Asis, S. E. *J. Chil. Chem. Soc.* **2006**, *51*, 859.
(8) Perrett, S.; Whitfield, P. J. *Planta Med.* **1995**, *61*, 276.
(9) (a) Schimitschek, E. J.; Trias, J. A.; Hammond, P. R.; Henry, R. A.; Atkins, R. L. *Opt. Commun.* **1976**, *16*, 313. (b) Bufe, M.; Wolf, T. *Phys. Chem. Chem. Phys.* **2006**, *8*, 4222.
(10) Barath, Z.; Radics, R.; Spengler, G.; Ocsovszki, I.; Kawase, M.; Motohashi, N.; Shirataki, Y.; Shah, A.; Molnar, J. *In Vivo* **2006**, *20*, 645.
(11) Reviews: (a) Ghosh, C. K. *J. Heterocycl. Chem.* **1983**, *20*, 1437. (b) Sabitha, G. *Aldrichimica Acta* **1996**, *29*, 15. (c) Ghosh, C. K.; Patra, A. *J. Heterocycl. Chem.* **2008**, *45*, 1529.

(12) (a) Ishar, M. P. S.; Kumar, K.; Singh, R. *Tetrahedron Lett.* **1998**, *39*, 6547. (b) Ghosh, T.; Bandyopadhyay, C. *Tetrahedron Lett.* **2004**, *45*, 6169.
(13) (a) Bandyopadhyay, C.; Sur, K. R.; Patra, R.; Banerjee, S. *J. Chem. Res.* **2003**, 459. (b) Bandyopadhyay, C.; Sur, K. R.; Patra, R.; Banerjee, S. *J. Chem. Res., Miniprint* **2003**, 847.
(14) (a) Singh, G.; Singh, R.; Girdhar, N. K.; Ishar, M. P. S. *Tetrahedron* **2002**, *58*, 2471. (b) Singh, G.; Singh, L.; Ishar, M. P. S. *Tetrahedron* **2002**, *58*, 7883. (c) Sattofattori, E.; Anzaldi, M.; Balbi, A.; Artali, R.; Bombieri, G. *Helv. Chim. Acta* **2002**, *85*, 1698. (d) Singh, G.; Singh, G.; Ishar, M. P. S. *Helv. Chim. Acta* **2003**, *86*, 169. (e) Singh, G.; Singh, G.; Ishar, M. P. S. *Synlett* **2003**, 256.
(15) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *Tetrahedron Lett.* **2009**, *50*, 3966.
(16) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *J. Heterocycl. Chem.* **2010**, *47*, 973.
(17) Singh, G.; Ishar, M. P. S.; Gupta, V.; Singh, G.; Kalyan, M.; Bhella, S. G. *Tetrahedron* **2007**, *63*, 4773.
(18) Maiti, S.; Lakshmykanth, T. M.; Panja, S. K.; Mukhopadhyay, R.; Datta, A.; Bandyopadhyay, C. *J. Heterocycl. Chem.* **2011**, in press; DOI. 10.1002/jhet.567.
(19) Maiti, S.; Panja, S. K.; Bandyopadhyay, C. *Tetrahedron* **2010**, *66*, 7625.
(20) (a) Boulton, A. J.; Mckillop, A. In *Comprehensive Heterocyclic Chemistry*, 1st ed., Vol. 2; Katritzky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, **1984**, Chap. 2.08, 396–510. (b) Keller, P. A. In *Comprehensive Heterocyclic Chemistry III*, 1st ed., Vol. 7; Katritzky, A. R., Ed.; Elsevier: Oxford, **2008**, Chap. 7.05, 217–307.
(21) Battistuzzi, G.; Bernini, R.; Cacchi, S.; Salve, I. D.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297.
(22) Park, S. J.; Lee, J.-C.; Lee, K.-I. *Bull. Korean Chem. Soc.* **2007**, *28*, 1203.
(23) Peters, J.-U.; Capuano, T.; Weber, S.; Kritter, S.; Sagesser, M. *Tetrahedron Lett.* **2008**, *49*, 4029.
(24) Kobayashi, Y.; Katagiri, K.; Azumaya, I.; Harayama, T. *J. Org. Chem.* **2010**, *75*, 2741.
(25) **Typical Experimental Procedure for the Rearrangement of 2-(*N*-Methyl-*N*-phenyl)aminochromone-3-carboxaldehyde (4a)**
Compound **4a** (0.14 g, 0.5 mmol) was heated under reflux in AcOH (3 mL) containing 4 drops of H_2O for 2 h when the absence of **4a** was observed by TLC. The reaction mixture was cooled to r.t. and poured into ice-cold water. The resultant acidic mixture was neutralized with $NaHCO_3$ when a solid began to precipitate. The precipitated solid was filtered, dried in air, and crystallized from benzene–light PE (2:1) to give pale yellow crystalline solid **6a**.
***N*-Methyl-3-salicyloyl-2-quinolone (6a)**
Yield 0.12 g (86%); mp 182–184 °C. IR (KBr): 3036, 1645, 1626, 1589 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.78 (s, 3 H, NCH_3), 6.81–6.87 (m, 1 H, 5′-H), 7.04 (br d, *J* = 8.1 Hz, 1 H, 3′-H), 7.28–7.34 (m, 1 H, ArH), 7.42–7.47 (m, 1 H, ArH), 7.49–7.54 (m, 2 H, ArH), 7.63–7.71 (m, 2 H, ArH), 7.86 (s, 1 H, 4-H), 11.96 (s, exchangeable, 1 H, OH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 114.3, 118.2, 118.9, 119.2, 119.4, 122.7, 129.8, 130.6, 132.3, 132.9, 136.9, 139.1, 140.5, 159.4, 162.9, 199.0. MS: *m/z* = 280 [M + H^+], 302 [M + Na^+]. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 73.11; H, 4.69; N, 5.02. Found: C, 72.92; H, 4.60; N, 4.97.
(26) (a) Nishiwaki, N. *Molecules* **2010**, *15*, 5174. (b) Croft, S. L.; Seifert, K.; Yardley, V. *Indian J. Med. Res.* **2006**, *123*, 399.