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SYNTHETIC CONNECTIONS TO THE AROMATIC DIRECTED METALATION REACTION. A MODIFIED von NIEMENTOWSKI QUINOLINE SYNTHESIS FROM ANTHRANILAMIDES

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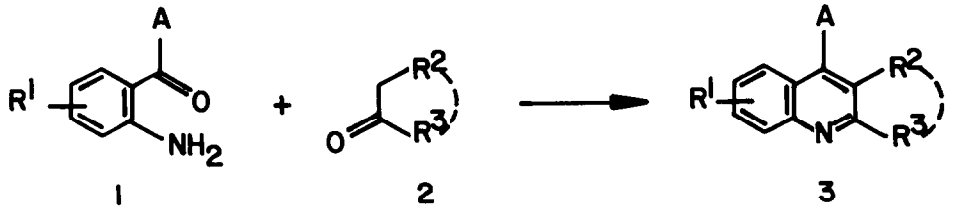
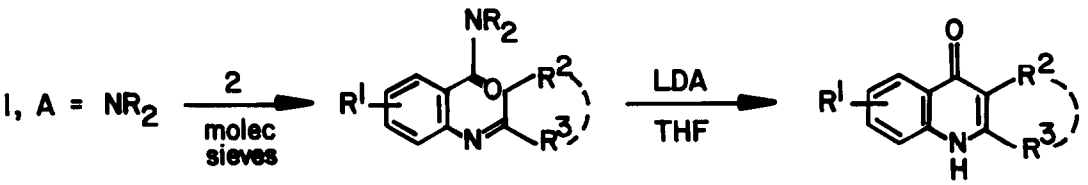
Summary: Anthranilamides **1**, A = NR_2 derived from benzamides by directed ortho metalation-amination, are converted into the corresponding imines **4** which upon treatment with LDA lead to substituted 4-quinolones **5** thus providing a general new quinoline synthesis **(Table).**

The classical Friedlander and the related Pfitzinger and von Niementowski reactions **(Scheme, 1 + 2 → 3)** constitute flexible methodologies for the construction of 1-, 3-, and 4- but not 5-, 6-, 7-, and 8- ring substituted quinolines owing to the poor accessibility of substituted o-amino carbonyl components **(1).** [1] We report on a variant of the von Niementowski synthesis via **4** leading to 4-quinolones **(5)** which a) is analogous to our recently reported anionic aromatic ring annelation of o-allyl benzamides;[2] and b) is based on the benzamide directed ortho metalation tactic[3] for the formation of the key anthranilamide precursors **1**, A = NR_2; and c) may be carried out under comparatively mild, base-catalyzed



1 2 3

A = H, R (Friedländer); A = CO_2Na ⟹ isatin (Pfitzinger); A = OH, OR (von Niementowski)



4 5

SCHEME

conditions. In view of the ready availability of substituted anthranilamides **1** by the regiospecific ortho metalation-amination sequence,[4] this methodology promises to be a generally useful modification of the von Niementowski process for quinoline ring construction.

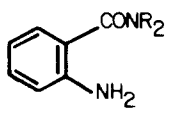
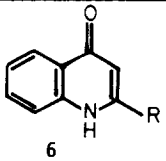
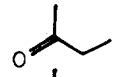
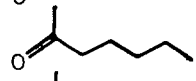
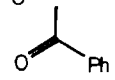
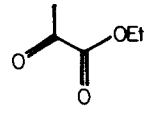
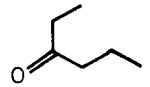
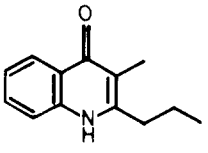
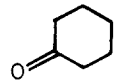
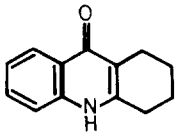
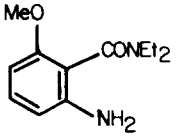
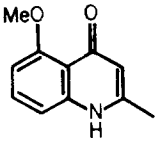
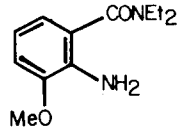
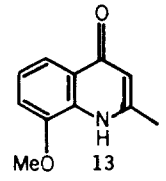
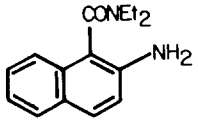
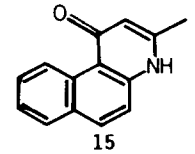
Anthranilamides **1,** A = NR_2[2] were converted into the corresponding imines **4** [5] which were inconvenient to purify and therefore were thoroughly dried and used directly in the heteroannelation reaction. Treatment of **4** with LDA (THF/0°C → RT or reflux) led to the 4-quinolones **5** in good to excellent yields. The results are summarized in the **Table.** A number of 2-substituted 4-quinolones **(6a-e)** are readily accessible under mild conditions including the 2-carboethoxy derivative **6e.** Steric effects to cyclization resulting from amide N-substitution appear not to be significant as evidenced from comparison of formation of **6a** from either the dimethyl **(1a)** or diethyl **(1b)** amide. Unsymmetrical ketones led regiospecifically to the 4-quinolone with the smaller 3-substituent, e.g. **6c** and **7.** Annelated products are easily obtained, e.g. **9.**

Of greater significance for the scope of this heteroannelation tactic are the smooth conversions of methoxy-substituted anthranilamides **10** and **12** into the corresponding 4-quinolones **11** and **13** bearing substituents on the benzene ring.[6] As an extension to more highly condensed systems, the 2-amino-1-naphthamide **14** was subjected to the two-step procedure to give the benzoquinolone **15** in good yield.

These observations coupled with the previous results of anionic o-allyl benzamide cyclizations[2] suggest the emergence of a chameleon character for the amide functionality: on the one hand, it resists nucleophilic attack by alkyllithiums and instead serves as a powerful ortho metalation director at low temperatures; on the other hand, it participates in intramolecular carbanionic attack at higher temperatures. Generalization and extension of the modified von Niementowski synthesis is in progress.[7]

Typical Procedure. A solution of 1.0 equiv. of the imine and 2.0 equiv. of LDA (obtained either as a 2.0 M solution in C_6H_{12} (Lithium Corp) or pre-formed from a solution of i-Pr_2NH in THF and n-BuLi in hexane) in THF (20 mL/mmol of imine) was mixed at 0°C under Ar. The resulting orange reaction mixture was stirred at the appropriate temperature (RT or at reflux) for 3-12 h. The reaction was then quenched with MeOH and the solvent was removed in vacuo. Salts were removed from the crude residue by filtration through silica gel usingCH_2Cl_2-MeOH (10:1). The filtrate was evaporated and the residue was purified by flash chromatography using CH_2Cl_2-MeOH or Et_2O-MeOH as eluant to give the pure product.

Table. Synthesis of 4-Quinolone Derivatives

Anthranilamide[a]	Carbonyl Compound	Reaction Conditions[b]	Quinolone Derivative[c]	Yield, %[d]	mp °C (lit mp)
					
1 (A = NR_2)			**6**		
1a (R = Me)		A	**6a** (R = Me)	45	233-235(MeOH/$CHCl_3$) (234-236)[e]
1b (R = Et)		A	**6a** (R = Me)	55	233-235 (234-236)[e]
1b		A	**6b** (R = Et)	95	176-177(Me_2CO) (180-181)[f]
1b		A	**6c** (R = n-Pentyl)	93	134-138(hex-CH_2Cl_2) (128)[g]
1b		A	**6d** (R = Ph)	70	249-250(EtOH) (250.3-250.7)[h] (259-260)[h]
1b		A	**6e** (R=CO_2Et)	64	213-217(CH_2Cl_2-MeOH) (214-215)[i]
1b		A	 **7**	58	254-258
1b	 **8**	B	 **9**	70	330-333 (MeOH-$CHCl_3$)
 **10**		C	 **11**	73	289-290(MeOH-Et_2O) (292)[j]
 **12**		A	 **13**	95	226-228 (229)[i]
 **14**		B	 **15**	84	345-347 (332-333)[k]

Footnotes to Table

[a] With the exception of N,N-diethyl anthranilamide, which was obtained by standard procedures, all the starting materials were prepared according to ref. 4. [b] Condition A: 0°C to room temperature, 8-12 h. Condition B: Heated at reflux for 8-12 h. Condition C: Heated at reflux for 3 h. [c] All new compounds show spectral (IR, NMR, MS) data consistent with the assigned structures. [d] All yields are of chromatographically pure materials. [e] Limpach, L. Chem. Ber. **1931,** 64, 969. [f] Austin, W.C.; Hunts, L.H.C.; Potter, M.D.; Taylor, E.P. J. Pharma. Pharmacol. **1959,** 11, 80. [g] Buu-Hoi, N.P.; Royer, R.; Xuong, N.D.; Jacquignon, P. J. Org. Chem. **1953,** 18, 1209. [h] Fuson, R.C.; Burness, D.M. J. Am. Chem. Soc. **1948,** 68, 1270. [i] Baker, J.T.; Duke, C.C. Austr. J. Chem. **1976,** 29, 1023. [j] Salzer, W.; Timmler, H.; Andersag, H. Chem. Ber. **1948,** 81, 12. [k] Desai, K.; Desai, C.M. Ind. J. Chem. **1967,** 5, 170.

References and Footnotes

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2. Sibi, M.P.; Dankwardt, J.W.; Snieckus, V. J. Org. Chem. **1986,** 51, 531.
3. Snieckus, V. Lect. Heterocyclic Chem. Suppl. J. Heterocyclic Chem. **1984,** 95; Beak, P.; Snieckus, V. Accts. Chem. Research, **1982,** 15, 306.
4. Reed, J.N.; Snieckus, V. Tetrahedron Lett. **1983,** 3795.
5. Imines were prepared by treatment of the anthranilamides at room temperature with the carbonyl compound as solvent (volatile ketones) for 2-7 days or in benzene at reflux (PhCOMe, cyclohexanone) for 2 days and were obtained generally in 85-95% (estimated by NMR). In view of their hydrolytic instability, the imines were dried at high vacuum and used immediately in the cyclization reactions.
6. Very few substituted anthranilic acid derivatives have been used in the original von Niementowski synthesis, see ref. 1, p 195.
7. We are grateful to NSERC Canada and Merck Frosst Canada for financial support of our synthetic programs.

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