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An Expedient Synthesis of Highly Functionalized Naphthyridones and Quinolines from a Common *N*-Aryl Pyridinone Template

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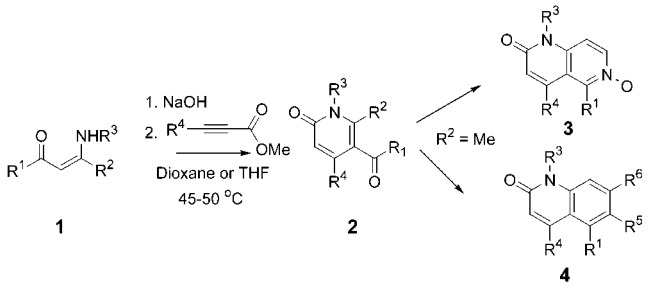
ABSTRACT



We describe herein a new base-mediated process for the formation of *N*-arylpyridinones 2 and their use for the preparation of naphthyridones and quinolines. The cyclization of various hindered enamines with methyl propiolate proceeds efficiently in the presence of NaOH to afford the corresponding *N*-arylpyridinones. These substrates were then found to undergo subsequent cyclizations to afford highly functionalized naphthyridones and quinolines.

Pyridinones, naphthyridones, and quinolines are important heterocyclic templates. Many members of this class of heterocycles have significant biological activity.[1,2] As a result, the preparation of these heterocycles has become of great interest for the design of potential pharmaceutical agents.[1−3] We recently required a flexible method for the preparation of several members of this class of compounds. While many of the known protocols are suitable for the preparation of the parent heterocycle (Scheme 1),[3] which can be functionalized in later steps, we found it cumbersome and sometimes

(1) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Ltd.: New York, 1996; Vols. 5 (quinolines) and 7 (naphthyridones).

(2) For pyridinones, see: (a) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002** ASAP April 5. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Averill, K. M.; Chan, D. M. T.; Combs, A. *Synlett* **2000**, *5*, 674−676. (c) Chiba, T.; Takahashi, T. *Chem. Pharm. Bull.* **1985**, *33*, 2731−2734. (d) Carlson, G. R. U.S. Patent 77-816051, 1980. For naphthyridones, see: (e) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329−5335. (f) Markgraf, J. H.; Snyder, S. A.; Vosburg, D. A. *Tetrahedron Lett.* **1998**, *39*, 1111−1112. (g) Sherlock, M. H.; Kaminski, J. J.; Tom, W. C.; Lee, J. F.; Wong, S. C.; Kreutner, W.; Bryant, R. W.; McPhail, A. T. *J. Med. Chem.* **1988**, *31*, 2108−2121. For quinolines, see: (h) Mederski, W. K. R., Lefort, M., Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757−12770. (i) Ogawa, H.; Miyamoto, H.; Kondo, K.; Yamashita, H.; Nakaya, K.; Tanaka, M.; Kitano, K.; Kan, K.; Tominaga, M.; Yabuuchi, Y. JP Patent WO 9401113, 1994. (j) Micheletti, R.; Doods, H. N.; Turconi, M.; Sagrada, A.; Donetti, A.; Schiavi, B. G. EP Patent 0382687A3, 1989.

(3) A review of the relevant literature indicated that although pyridinones had been formed from enamines and methyl propiolate, the *N*-aryl variant had not been reported: Singh, B.; Lesher, G. Y.; Pluncket, K C.; Pagani, E. D.; Bode, D. C.; Bentley, R. G.; Connel, M. J.; Hamel, L. T.; Silver, P. J. *J. Med. Chem.* **1992**, *35*, 4858−4865 and references herein. Also, *N*-alkyl β-amino ester and *N*-aryl β-enaminonitrile derivatives were shown to efficiently undergo cyclization with unsaturated esters, whereas ketone analogues proceeded in very low yield: (a) Erian, A. W.; Ali, M. S.; Mohamed, N. R.; Gad, W. A.; Nada, A. A. *Sci. Pharm.* **1999**, *67*, 253−262. (b) Wang, M.-X.; Miao, W.-S.; Cheng, Y.; Huang, Z.-T. *Tetrahedron* **1999**, *55*, 14611−14622. (c) Caballero, E.; Madrigal, B.; Medarde, M.; Puebla, P.; Honores, Z.; Martin, E.; San Feliciano, A. *ACH−Models Chem.* **1998**, *135*, 457−473.

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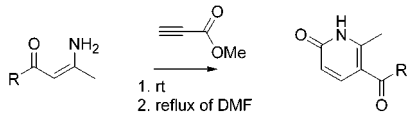
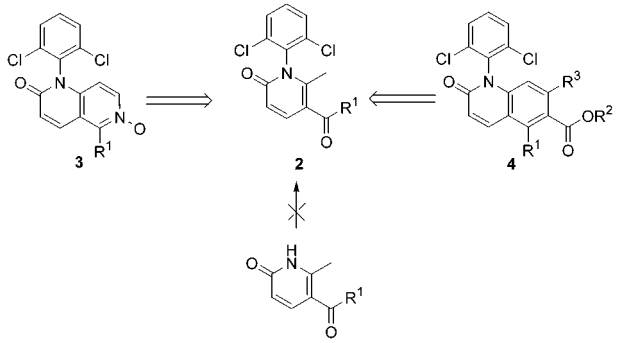
Scheme 1



impossible to prepare several desired quinolines and naphthyridones of interest. In particular, naphthyridones and quinolines containing a sterically hindered aryl group on the amide nitrogen were not accessible by these approaches (Scheme 2). Because this functionality could not be added

Scheme 2



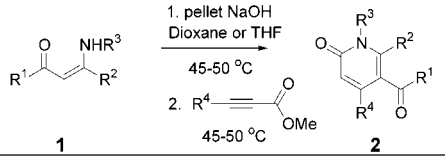
on the amide moiety at a later stage of the synthesis, we needed to design a new route that would incorporate the aryl group in the early stages of the synthesis. We envisioned a strategy involving the preparation of *N*-arylpyridinones as templates, which could serve as precursors to the highly functionalized naphthyridone and quinoline bicyclic derivatives. In this communication we report a base-mediated synthesis of *N*-arylpyridinones from 1,3-diketones, methyl propiolate, and the corresponding aniline and demonstrate their use in the efficient syntheses of naphthyridones and quinolines.

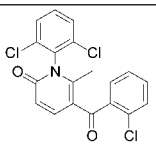
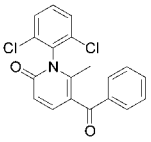
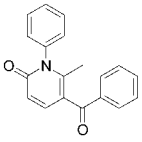
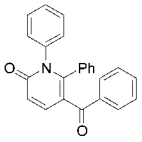
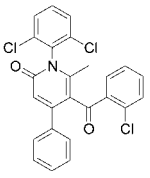
We initiated our investigation by preparing various *N*-aryl enamines of 1,3-diketones and investigated their subsequent reaction with methyl propiolate and other appropriate Michael acceptors. Sterically hindered enamines **1a,b** were obtained upon Dean Stark condensation of the ketone and 2,6-dichloroaniline with catalytic amount of *p*-TsOH in high yields.[4] These compounds were crystallized from the reaction mixture and used without further purification. Enamines **1c,d** were obtained following the known literature procedures.[5]

(4) For reviews on the preparation of enamines: (a) Haynes, L. W. In *Enamines: Synthesis, Structure, and Reactions*; Cook, A. G., Ed.; Marcel Dekker: New York, 1969; pp 55−100. (b) Pitacco, G.; Valentin, E.; In *The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1982; Part 1, Chapter 15, pp 624−714. (c) Boatman, S.; Hauser, C. R. *J. Org. Chem.* **1966**, *31*, 1785−1788. For a review on the addition of amines to triple bonds: Chekulaeva, I. A.; Kondrat'eva, L. V. *Russ. Chem. Rev.* **1965**, *34*, 669.

(5) (a) Maroni, P.; Cazaux, L.; Tisnes, P.; Zambeti, M. *Bull. Soc. Chim. Fr.* **1980**, *2*, 179−186. (b) Tsuge, O.; Koga, M.; Shinkai, I. *Tetrahedron* **1973**, *29*, 259−265.

Table 1. Synthesis of *N*-Arylpyridinones



entry /**1a-d**	R^1	R^2	R^3	R^4	product	yield (%)
1 **1a**		Me		H	 **2a**	60
2 **1b**	Ph	Me		H	 **2b**	67
3 **1c**	Ph	Me	Ph	H	 **2c**	55
4 **1d**	Ph	Ph	Ph	H	 **2d**	70
5 **1a**		Me		Ph	 **2e**	51

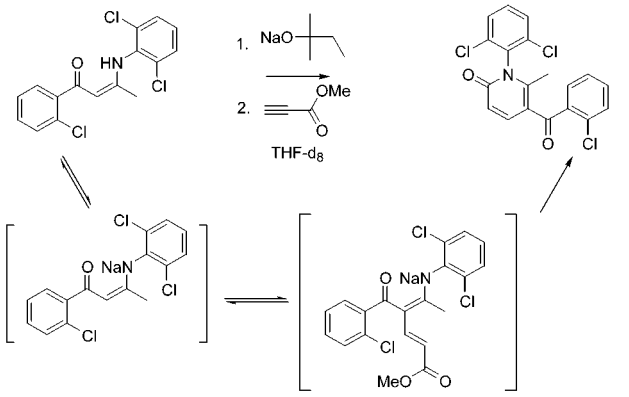
The subsequent cyclization of the *N*-aryl enamine **1a** was next investigated. Employing the literature conditions[3] (room temperature to 100 °C in dioxane or DMF), we were unable to observe any of the desired *N*-arylpyridinone. However, we could effect the cyclization of enamine **1a** to *N*-arylpyridinone **2a** in 50% yield by heating the mixture to 140 °C for 5 days. Under these reaction conditions, an excess of methyl propiolate was required. Indeed, the desired cyclization of the enamine to the methyl propiolate was competing with the thermal cyclotrimerization of methyl propiolate, giving benzene tricarboxylate as a substantial byproduct. To improve the reaction conditions and yields, the influence of Lewis acid catalysts (BF_3 etherate, $ZnCl_2$, $Ti(O\text{-}i\text{-}Pr)_4$) on the cyclization reaction was investigated with moderate success. We were able to reduce the reaction time to 1−2 days by using catalytic amount of *p*-TsOH or

$MeSO_3H$ and heating in DMAc, but the required temperatures were still very high and resulted in undesired triester.

We next turned our attention to base catalysis. We were pleased to find that premixing the enamine **1a** with either Na-*tert*-pentoxide or NaOH in THF, followed by adding methyl propiolate, led to a much cleaner reaction at 50 °C. Most importantly, the problematic benzene tricarboxylate was not produced under these conditions. Other bases (NaOMe, NaH, LiHMDS, KHMDS, Et_3N, pyridine, DABCO, and DBU) did not lead to improved reactions. The best results were obtained using NaOH to provide the desired pyridone **2a**−**e** in 51−70% yield (Table 1).

The cyclization is believed to occur via a stepwise mechanism: Michael addition of the deprotonated enamine to methyl propiolate followed by amide formation (Scheme 3). The intermediate **5** resulting from the Michael addition

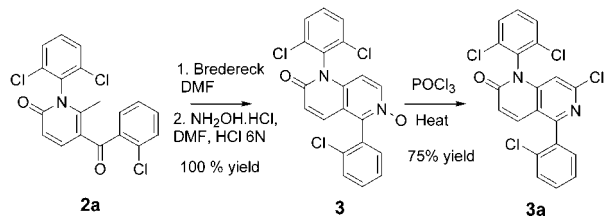
Scheme 3



of the enamine to methyl propiolate could be detected by HPLC/MS, and the structure of the *trans* adduct was confirmed by NMR.[6]

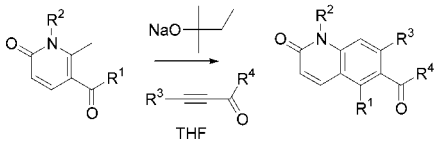
With a variety of key pyridinones in hand, we next turned our attention to naphthyridone and quinoline formation. We developed a one-pot, two-step protocol to provide the desired naphthyridones (Scheme 4). First, *N*-arylpyridinone **2a** was

Scheme 4

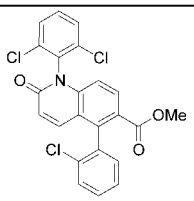
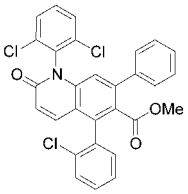
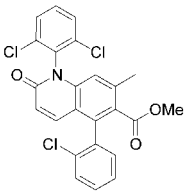


treated with Bredereck's reagent[7] in DMF to afford the

Table 2. Synthesis of Quinolines



R^1 = 2-chlorophenyl; R^2 = 2,6-dichlorophenyl

entry	R^3	R^4	product	isolated yield (%)
1	H	OMe	 **4a**	91
2	Ph	OMe	 **4b**	55
3	Me	OMe	 **4c**	48

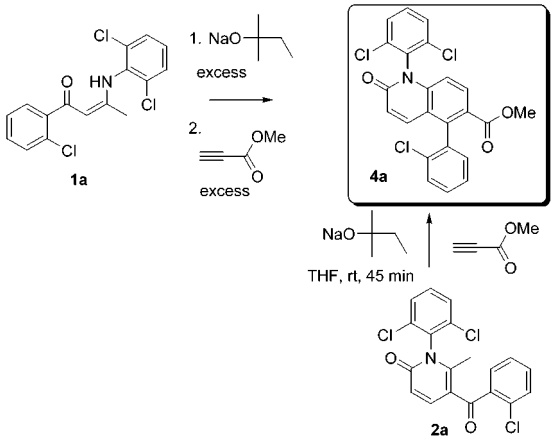
desired *N*,*N*-dimethyl enamine intermediate. This crude enamine was then treated with $NH_2OH{\cdot}HCl$ in DMF, and the corresponding naphthyridone *N*-oxide **3** was precipitated quantitatively out of water. It was possible to synthesize the parent naphthyridone by substituting ammonium acetate for $NH_2OH{\cdot}HCl$; however, preparing the *N*-oxide opened room for further functionalization of the naphthyridone ring. Indeed, the naphthyridone *N*-oxide **3** could be further functionalized by treatment with neat $POCl_3$ to afford chloronaphthyridone **3a** in 75% yield. 2-Chloronaphthyridone **3a** could be further functionalized by various transition-metal-catalyzed cross-coupling reactions yielding 2-C and N-substituted naphthyridones. This further demonstrates the versatility of this methodology to prepare highly functionalized naphthyridones.

During the course of our study of the sodium-*tert*-pentoxide mediated cyclization of enamine **1a** and methyl propiolate, a byproduct was observed. This product was determined to be quinoline **4a** and was formed in 41% unoptimized yield using an excess of methyl propiolate and base. Although this yield is marginal, it represents a one-pot synthesis of a quinoline from an enamine and methyl propiolate. Further investigation showed that *N*-arylpyridinones **2a** in the presence of sodium-*tert*-pentoxide and methyl propiolate led to the same product in 91% yield at room

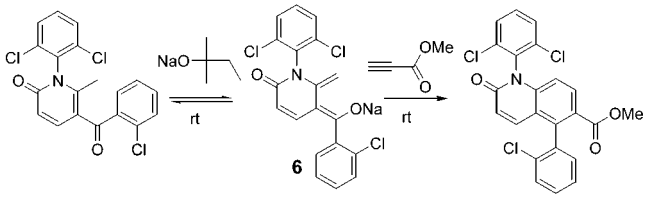
(6) The protonated form of intermediate **5** was identified after quenching with TFA. See Experimental Section for details.

(7) For a similar use of the Bredereck's reagent, see ref 3.

Scheme 5



Scheme 6



temperature (Scheme 5). Disubstituted alkynes could also be reacted with *N*-arylpyridinone, yielding other substituted quinolines **4b,c** albeit in lower yields (Table 2).

A proposed mechanism for the quinoline synthesis is depicted in Scheme 6. The sequence is triggered by deprotonation of the α-methyl group, which produces a vinologous enolate. This enolate then reacts with methyl propiolate by either a concerted reaction or a stepwise Michael addition−aldol condensation. NMR experiments confirmed the formation of the vinologous enolate **6** when *N*-arylpyridinone **2a** was treated with sodium-*tert*-pentoxide in THF-d_8.

In summary, we have demonstrated a base-mediated synthesis of *N*-arylpyridinones under mild conditions and demonstrated their use for the preparation of *N*-arylnaphthyridones and quinolines. These protocols are especially attractive as they allow for the synthesis of these specifically functionalized heterocycles in very few steps. Expanding the scope of this methodology to include hindered tertiary alkyl substituents as well as applying it to the synthesis of other interesting heterocycles will be the focus of future work.

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Supporting Information Available: Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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