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An efficient catalytic method for the Friedländer annulation mediated by peptide coupling agent propylphosphonic anhydride (T3P®)

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ABSTRACT

We have demonstrated the utilization of T3P, a mild and low toxic peptide coupling agent, as a promoter and water scavenger in the Friedländer annulation, and thus introduced a highly efficient catalytic process to access carbocyclic and heterocyclic fused quinolines under microwave irradiation or a conventional heating technique. The reaction conditions are sufficiently mild to tolerate the acid and base sensitive functional groups that can serve as levers for further extension of the quinoline products.

Quinolines and their derivatives are very significant structural motifs that occur widely in natural[1] and synthetic products, often displaying a broad range of biological activity. Members of this family have wide applications in medicinal chemistry, being used as antimalarial,[2] antituberculosis,[3] antibacterial,[4] anti-inflammatory,[5] antiviral,[6] antihypertensive,[7] and as tyrosine kinase inhibiting agents.[8] In addition to the medicinal applications, quinolines have been employed in the study of bioorganic and bioorganometallic processes.[9] Due to their broad range of applicability in medicinal, industrial, bioorganic as well as in the fields of synthetic organic chemistry, there has been an increasing interest in developing efficient methods for quinoline synthesis.

The Friedländer quinoline synthesis[10] is one of the simplest and powerful tools for the synthesis of quinolines. In its most classical and general form, the Friedländer reaction involves condensation between 2-aminoaryl carbonyl compound (aldehyde or ketone) and a second carbonyl compound containing a reactive α-methylene group followed by cyclodehydration. The reaction can be promoted by acid or base catalysis, or by heating a mixture of the reactants at 150–220 °C in the absence of a catalyst.[11] Many of these procedures, however, have drawbacks such as poor functional group tolerance, limited substrate scope, and difficulties in the work-up procedures. For instance, under thermal or basic conditions, *ortho*-aminobenzophenones failed to react with simple ketones such as cyclohexanone and β-keto esters.[12] Likewise, a carboxylate functionality was not tolerated under basic conditions.[13] In an attempt to improve on these procedures, Lewis acid catalyzed methods for quinoline synthesis have recently been reported.[14] Yet, some of these procedures suffered from harsh reaction conditions, low yields, and the use of stoichiometric and/or expensive reagents. And in some cases, high catalyst loading had to be employed in order to attain respectable yields. Thus, the development of highly efficient catalytic methods having broad substrate and functional group tolerance for the synthesis of quinolines is still vital.

Propylphosphonic anhydride (T3P®) is an efficient and mild peptide coupling reagent having low toxicity and low allergenic potential.[15] Its water scavenging and coupling capabilities have generated innovative uses for this reagent beyond peptide synthesis.[16] There are quite a few examples, wherein, T3P is utilized in dehydration chemistry,[17] and molecular rearrangements.[18] Of late, T3P has been used as a reagent in the preparation of various functionalized heterocycles.[19] Herein, we report our results on the highly effective T3P catalyzed Friedländer annulation of quinolines and polycyclic quinolines under microwave irradiation and a conventional heating technique.

The preparation of **3a** from 2-acetylaniline (**1a**) was chosen as a model reaction to assess the competency of T3P in promoting the Friedländer reaction (Table 1). The initial experiments were carried out with equimolar amounts of **1a**, cyclohexanone (**2a**) in solution in DMF with T3P (50% solution in EtOAc) at room temperature. As these conditions led to a slightly lower yield of **3a** (Table 1, entry 1), the mixture was heated to 90 °C. We were interested to find

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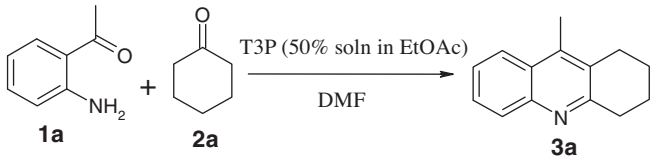
Table 1
Screening optimal conditions



Entry	T3P (mol %)	Time (h)	Temp (°C)	Yield (%) **3a**
1	100	12	25	21
2	100	4	90	98
3	50	4	90	98
4	25	6	90	98
5	20	6	90	98
6	15	11	90	94
7	20	0.5	90	97[a]
8	10	1	100	88[a]
9	—	1	120	0[a,b]

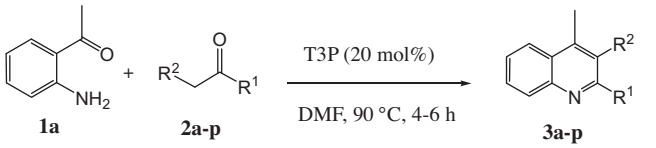
[a] Reaction was performed under MW irradiation.
[b] Intermediate Schiff base was observed in trace.

that complete consumption of the starting material occurred in 4 h to provide tetrahydroacridine **3a** in 98% yield (Table 1, entry 2). Upon reinvestigation (see Table 1), it was found that 20 mol % of T3P at 90 °C was also efficient to afford **3a** in respectable yield (Table 1, entry 5). Decreasing the amount of T3P from 20 to 15 mol % prolonged the duration of reaction in addition to lowering the yield of quinoline to some extent (Table 1, entry 6). Moreover, it is noteworthy that this reaction could be run under microwave irradiation without loss of efficiency in a much shorter duration (Table 1, entry 7). As observed from Table 1 (entries 7 and 8), it was essential to use 20 mol % of T3P under microwave irradiation to obtain optimum conversion of **1a**. Further, there was no product when the reactants were irradiated under microwave conditions at 120 °C in DMF in the absence of T3P (Table 1, entry 9), but the intermediate Schiff base was observed in trace.

Among the solvents screened (THF, DMF, dioxane, toluene, MeCN, EtOAc, and NMP), most of them supported the reaction, DMF and NMP were demonstrated as the best solvents. The high efficiency of T3P catalyzed quinoline synthesis was then established by reacting **1a** with structurally diverse carbonyl compounds containing a reactive α-methylene group under the optimized thermal conditions (DMF, 20 mol % of T3P, 90 °C, conventional heating) and the results are summarized in Table 2. As shown in Table 2, this method was equally effective for both cyclic and acyclic ketones to generate a variety of quinoline derivatives. The present protocol was free from side reactions, such as self-condensation of ketones, which were normally observed under basic conditions and excellent isolated yields were observed for all substrates employed. It is noteworthy that the reaction tolerated both an acid sensitive (Table 2, entries 5 and 6) and base sensitive (Table 2, entries 9 and 10) functional groups to provide the respective quinolines in good yields.

The Friedländer reaction, depending upon the nature of catalyst, with unsymmetrical ketones such as ethyl methyl ketone is known to undergo two possible modes of cyclization producing distinct regioisomers viz., 2-ethylquinoline and 2,3-dimethylquinoline, respectively.[11] While under acidic conditions, 2,3-dimethylquinoline was reported as the major product along with minor amounts of 2-ethylquinoline, under basic conditions, 2-ethylquinoline was reported as the major isomer along with minor amounts of 2,3-dimethylquinoline. Surprisingly, the T3P catalyzed Friedländer reaction with unsymmetrical ketones afforded regiospecifically the 2,3-dialkylquinolines as exclusive products in excellent yields (Table 2, entries 13 and 14). No trace of the isomeric 2-alkylquin-

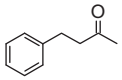
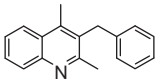
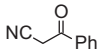
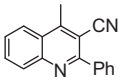
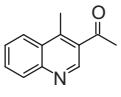
Table 2
T3P catalyzed quinoline synthesis: scope of ketones



Entry	Substrate	Product	Yield[a] (%)
1	**2a**	**3a**	98
2	**2b**	**3b**	98
3	**2c**	**3c**	96
4	**2d**	**3d**	97
5	**2e**	**3e**	94
6	**2f**	**3f**	95
7	**2g**	**3g**	98
8	**2h**	**3h**	96
9	**2i**	**3i**	97
10	**2j**	**3j**	90
11	**2k**	**3k**	98
12	**2l**	**3l**	96
13	**2m**	**3m**	98

(*continued on next page*)

Table 2 (*continued*)

Entry	Substrate	Product	Yield[a] (%)
14	 **2n**	 **3n**	99
15	 **2o**	 **3o**	95
16	 **2p**	 **3p**	79

[a] Isolated yields.

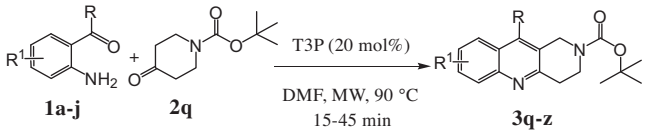
oline could be identified in ^{1}H NMR of the crude product before purification by crystallization. A related trend was observed in the case of an unsymmetrical cyclic ketone **2f** which gave rise exclusively to polycyclic quinoline **3f** (Table 2, entry 6). This phenomenon could be attributed to relatively mild reaction conditions and the absence of a Brönsted or Lewis acid catalyst. Under essentially the same conditions, the ketone bearing a terminal alkyne (**2p**) gave exclusively the unexpected quinoline **3p** in 79% yield (Table 2, entry 16).

The substrate scope of the reaction was further explored by performing the reaction between a fairly acid sensitive *N*-Boc keto derivative **2q** with a variety of 2-aminoaryl carbonyls (**1a**–**j**) under the optimized MW conditions[20] (DMF, 20 mol % of T3P, 90 °C) and the results are depicted in Table 3. As observed from Table 3, various substituted aromatic/heteroaromatic aldehydes and ketones reacted smoothly with **2q** to produce a range of quinoline derivatives. The reactions were quick (15–45 min) and good to excellent isolated yields were observed for all substrates employed. However, the reaction did not tolerate an *ortho*-aminoaryl aldehyde bearing an activated halogen on the ring (Table 3, entry 10), but gave the hydrolyzed product **3z**. In most cases (Tables 2 and 3), the solid products were isolated by simple aqueous work-up, and finally crystallized.

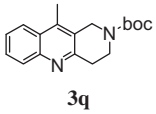
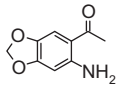
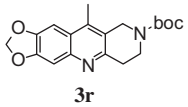
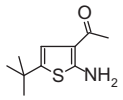
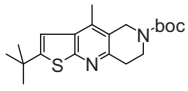
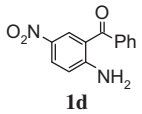
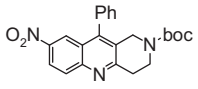
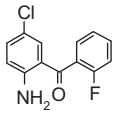
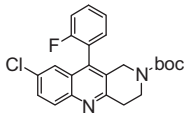
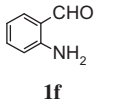
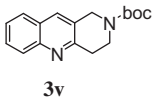
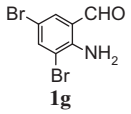
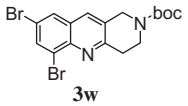
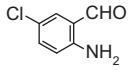
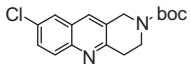
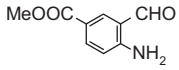
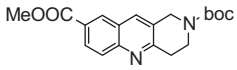
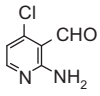
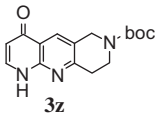
The enhanced catalytic activity of T3P in promoting the Friedländer annulation could be explained by the transformations shown in Scheme 1. A possible participation of T3P (**4**) during the commencement of reaction between **1** and **2** enhances the rate of formation of Schiff base (**7**) via the intermediate **5**. The 'open' hydrated T3P (**6**) produced during the process cyclizes to regenerate the catalyst **4** (T3P), which in turn, promotes an intramolecular aldol-type reaction to produce the intermediate **9**. Subsequent expulsion of quinoline **3** from the intermediate **9** produces **6**, and the catalytic cycle then continues by the regeneration of T3P in the process.

In conclusion we have demonstrated the utilization of T3P, a mild and low toxic peptide coupling agent, as a promoter and water scavenger in the Friedländer annulation, thus introduced a highly efficient catalytic method to access carbocyclic and heterocyclic fused quinolines under microwave irradiation[21] and a conventional heating technique.[22] The method, which uses cheap and readily available T3P, not only provides an excellent complement to quinoline synthesis, but also avoids the use of hazardous acids or bases. Further, the reaction conditions are sufficiently mild to tolerate acid or base sensitive functional groups that can serve as levers for further extension of the quinoline products. The high yields of products, easy workup procedure, broad functional group tolerance and use of only a catalytic amount of T3P make this process a complementary and/or superior method for the Friedländer quinoline synthesis.

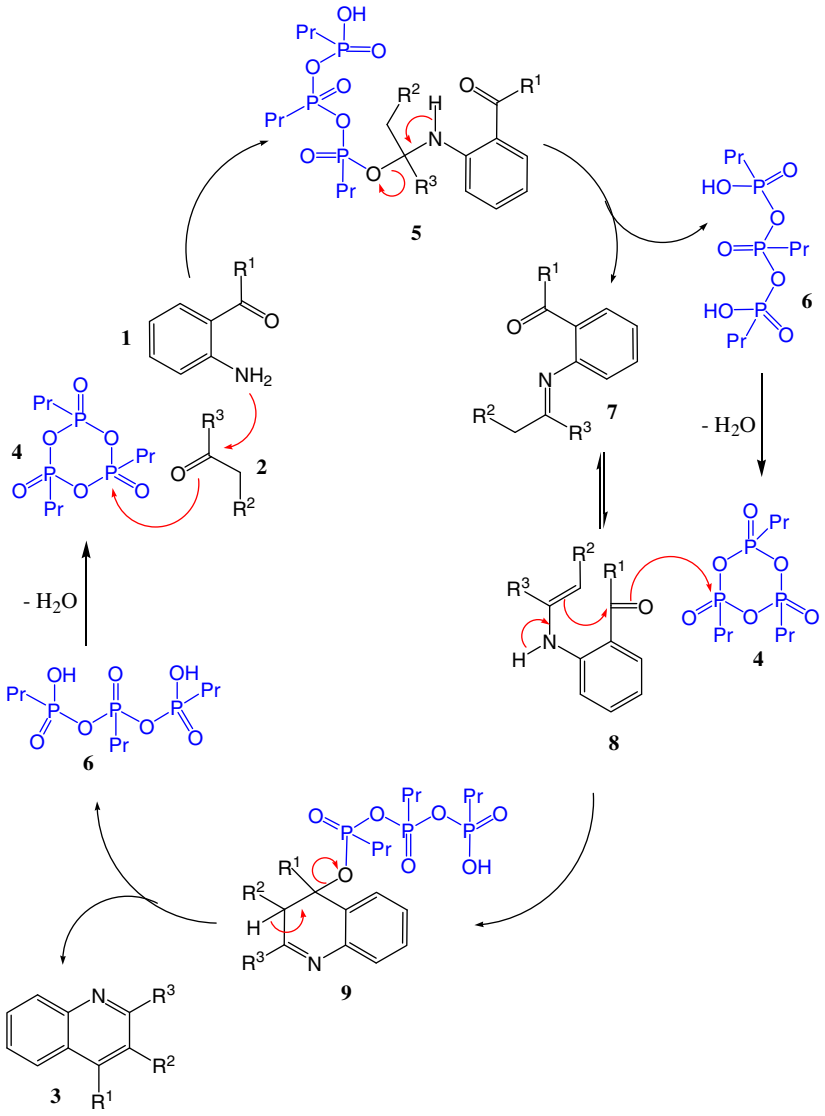
Table 3
T3P catalyzed quinoline synthesis: scope of 2-aminoaryl carbonyls



1a-j **2q** **3q-z**

Entry	Substrate	Product	Yield[a] (%)
1	 **1a**	 **3q**	96
2	 **1b**	 **3r**	94
3	 **1c**	 **3s**	89
4	 **1d**	 **3t**	98
5	 **1e**	 **3u**	95
6	 **1f**	 **3v**	97[b]
7	 **1g**	 **3w**	96[b]
8	 **1h**	 **3x**	98[b]
9	 **1i**	 **3y**	94[b]
10	 **1j**	 **3z**	73[b]

[a] Isolated yields.
[b] Reaction was completed in 15 min.



Scheme 1. Proposed mechanism of the T3P catalyzed quinoline synthesis.

Supplementary data

Supplementary data (copies of ^{1}H NMR, ^{13}C NMR and LCMS report for **3a**–**z**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.048.

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20. The microwave chemistry was performed on a single-mode microwave reactor Emrys™ Optimiser from Personal Chemistry in sealed reaction vessels.
21. *T3P catalyzed synthesis of quinolines under MW irradiation*: To a mixture of 2-aminoaryl ketone/aldehyde (**1**, 0.01 mol) and ketone (**2**, 0.01 mol) in DMF (8 mL) in a 20 mL microwave reaction vessel was added T3P (20 mol %, 50% soln in EtOAc). The resulting reaction mixture was irradiated with stirring in a microwave reactor (Emrys™ Optimiser from Personal Chemistry, 300 W) at 90 °C for 15–45 min. When the reaction was completed (monitored by TLC), the solvent was removed under vacuum and the residue was diluted with water (20 mL). The solid product which separated out was filtered, washed with water, and dried to afford the desired quinolines in good purity. The oily quinolines were extracted with ethyl acetate (2 × 15 mL) and the combined organic phase was washed with saturated $NaHCO_3$ solution (1 × 10 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was passed through a small plug of silica to afford the quinolines in good purity and yield.
22. *T3P catalyzed synthesis of quinolines under conventional heating*: To a mixture of 2-aminoaryl ketone/aldehyde (**1**, 0.01 mol) and ketone (**2**, 0.01 mol) in DMF (10 mL) was added T3P (20 mol %, 50% soln in EtOAc). The resulting reaction mixture was stirred at 90 °C for 4–6 h under conventional heating. When the reaction was completed (monitored by TLC), the solvent was removed under vacuum and the residue was diluted with water (20 mL). The solid product which separated out was filtered, washed with water, and dried to afford the desired quinolines in good purity. The oily quinolines were extracted with ethyl acetate (2 × 15 mL) and the combined organic phase was washed with saturated $NaHCO_3$ solution (1 × 10 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was passed through a small plug of silica to afford the quinolines in good purity and yield.