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LETTER

Friedländer synthesis of polysubstituted quinolines and naphthyridines promoted by propylphosphonic anhydride (T3P®) under mild conditions†

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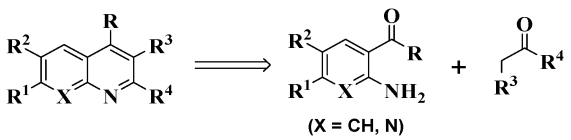
A new convenient, efficient and environmentally eco-friendly protocol for Friedländer synthesis of polysubstituted quinolines and naphthyridines is described. A wide variety of new products were readily prepared in the presence of propylphosphonic anhydride (T3P®) in short reaction times and excellent yields under mild conditions.

The construction of quinoline moieties has received great attention in the field of medicinal chemistry due to their biological activity.[1] A large variety of quinoline derivatives have been identified among privileged ones in drug discovery[2] and used as antiasthmatic, anti-inflammatory, antibiotic, antimicrobial, antibacterial, antiplatelet, antimalarial, insecticidal agents and tyrosine kinase inhibiting agents.[3] The quinoline scaffold is also found in many natural compounds, particularly in alkaloids.[4] In addition, quinolines have been employed in the study of bioorganic and bioorganometallic chemistry.[5] Consequently, a variety of elegant methods leading to these heterocyclic nuclei have been developed in the literature.[6] Among these methods, the Friedländer reaction[6f,g] is a straightforward method for preparing the polysubstituted quinolines and related azaheterocycles (Scheme 1).

The propylphosphonic anhydride (T3P®) catalyst represents an important and powerful tool for the promotion of one-pot synthesis of fused heterocycles from readily available starting materials, the use of which in the organic chemistry as a mild water scavenger in organic synthesis has increased rapidly in recent years.[7] In addition, T3P® is highly reactive and commonly used as a coupling agent and offers several advantages over traditional reagents, such as low toxicity, commercial scale availability, low price, low epimerization tendency, high selectivity yields, excellent purity, broad functional group, easy work up procedures due to water-soluble byproducts.[8] Further, a large number of new applications for the non-toxic nature of T3P® have recently been developed in the literature.[9]



Scheme 1 Friedländer annulation.

The Friedländer reaction is usually carried out either by heating an aqueous or alcoholic solution at reflux or by heating the abovementioned reagents at high temperature in the absence of catalysts.[10] However, originally strong bases were needed.[11] Under thermal or base catalysis conditions, 2-aminobenzophenone failed to react with simple ketones such as cyclohexanone and β-keto-esters.[12] In addition, changed methods employing iodine, Lewis acid, inorganic salts and a combination of acidic catalysts were most frequently used but the reaction has also been described with BrØnsted acidic catalysts, in a microwave oven, or in ionic liquids, all methods were widely used for the Friedländer annulation.[13] Unfortunately many of the reported methods suffered from harsh reaction conditions, the use of high reaction temperatures (up to 250 °C) and prolonged reaction times leads to several side products, harmful organic solvents, low product yields, tedious work-up procedure, no compliance with the green chemistry protocols, low selectivity, required chromatographic isolation technique, the use of stoichiometric and relatively expensive reagents and some of these catalysts present limitations due to the use of toxic and corrosive reagents. Moreover, the reaction has been performed in the presence of solvent such as DMSO or DMF leading to complex isolation and recovery procedures.

In this communication, we report a rapid, convenient and efficient one-pot synthesis of new polysubstituted quinolines and naphthyridines *via* Friedländer reaction performed without added solvent, using T3P® as a promoter, an environmentally benign and neutral catalyst under mild conditions.

In order to find the best reaction conditions for the synthesis of quinoline derivatives, 2-amino-5-chlorobenzophenone and cyclohexanone were chosen as model substrates to optimize the reaction conditions (Table 1). However, under solvent-free conditions, the reaction did not proceed when the mixture was heated at 50 °C in an oil-bath for 1 hour in the absence of

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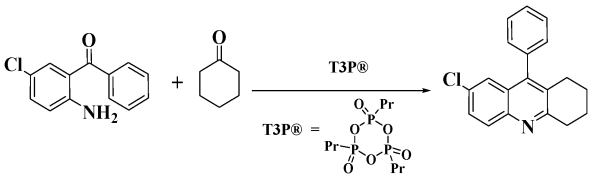
† Electronic supplementary information (ESI) available: Compounds full characterization and NMR spectra. See DOI: 10.1039/c2nj21043f

Table 1 Optimization of the reaction conditions



Entry	*t*/h	*T*/°C	T3P® (equiv.)	Conversion[a] (%)
1	1	50	0	Traces
2	1	50	0.1	17
3	1	50	0.2	32
4	1	50	0.5	63
5	1	50	0.8	95
6	1	50	1	100
7	0.5	50	1	96
8	**0.5**	**60**	**1**	**100**[b]
9	0.5	25	1	77
10	4	25	1	89
11	8	25	1	100
12	5 min[c]	100	1	100
13	5 min[c]	100	0.5	100[d]

[a] Determined by HPLC and LC-MS analysis. [b] Isolated in 95% yield. [c] The reaction was performed under microwave irradiation. [d] Quantitative yield was obtained.

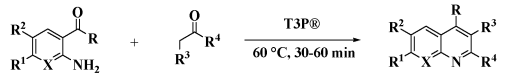
T3P® (Table 1, entry 1). In order to establish the effectiveness of the catalyst under the same conditions, weak conversion, above 17% detected by LC/MS, was obtained with 0.1 equiv. of T3P® (50% solution in EtOAc) (Table 1, entry 2). Then, upon increasing the amount of T3P® the conversion slightly increased to become total with 1 equiv. of T3P® (Table 1, entries 2–6). Further optimization showed that change of the reaction conditions (time, temperature) was appropriate for the cyclodehydration in good to excellent conversion (Table 1, entries 7–11). A full conversion was obtained at 60 °C for 30 minutes with a 95% isolated yield of quinoline (Table 1, entry 8). Nevertheless, performing the reaction in the presence of catalytic amounts of T3P® under microwave conditions at 100 °C for a power of 100 watts affords a total conversion after only 5 minutes (Table 1, entries 12 and 13). However, the conditions chosen to explore the scope of this protocol were 60 °C, 30–60 minutes and 1 equiv. of T3P® (entry 8) because this process is easy to scale up and widely accessible to all chemists.

More recently, the synthesis of various polysubstituted quinoline compounds prepared by the same reaction type in the presence of T3P® and DMF as the solvents under heating or microwave irradiation conditions was reported by Augustine and co-workers.[14] However, in this manuscript, we reported 29 interesting new compounds prepared under solvent-free conditions at 60 °C with short reaction times compared to the conventional heating method or under microwave irradiation.[14] In addition, this procedure is interesting as it shows that microwave heating is not always necessary to reach high conversions and excellent yields. After establishing the optimal reaction conditions, the substrate scope is explored. The generality of this reaction is illustrated with respect to various 2-aminoaryl ketones and a wide array of α-methylene ketones and the detailed results for these reactions are collected in Table 2.

Firstly, we turned our attention to examining the scope of the reaction between the cyclic mono-functionalized ketones and 2-aminoarylketones. Excellent yields of tricyclic quinolines were obtained in short reaction times (Table 2, entries 1–3). To our delight, a variety of aromatic, heteroaromatic, bicyclic and heterobicyclic ketones such as α-tetralone, chromanone, dihydrobenzofuranone, and dihydrobenzothiophenone derivatives also underwent smooth condensation with 2-aminoaryl ketones to afford the respective quadricyclic quinolines in excellent yields (Table 2, entries 14–17 and 24–26). In addition, other functionalized ketones, such as ethyl pyruvate, diethyl 1,3-acetonedicarboxylate, *tert*-butyl and ethyl acetylacetate derivatives, were also investigated in the presence of T3P® full conversion and satisfactory results were obtained (Table 2, entries 8–12 and 21–23).

However, compounds bearing acid sensitive functional groups such as the ethyl ester and *N*-boc also gave excellent yields with no sign of hydrolysis or deprotection, indicating the mild nature of the conditions (Table 2, entries 4 and 5). The quinoline resulting from cyclization through the terminal CH_3 of the methylketone was obtained in excellent yields (Table 2, entry 18) showing the powerful effect of T3P® in the synthesis of quinolines. Furthermore, the Friedländer reaction with unsymmetrical ketones afforded regiospecifically only one regioisomer in satisfactory yields in contrast to results obtained under acidic or basic conditions (Table 2, entries 8–11).[15] Theoretically, the Friedländer reaction with unsymmetrical 1,3-diones (containing 4 α-positions of a ketone) can have four possible routes for cyclisation, giving rise to four regioisomers. Surprisingly, the reaction afforded only one regioisomer in excellent yields (Table 2, entry 13). The observed regioselectivity of the cyclization could be explained by steric effects. This can be rationalized by the preferred imine/enamine formation of the carbonyl group next to the methyl group rather than the carbonyl group next to the phenyl group. Interestingly, in the case of α-bromoketone (Table 2, entries 19 and 20), 3-bromo-2,4-diarylquinoline is formed in excellent yields showing the high reactivity of T3P® used as the reaction promoter.[16] Thus, 3-bromoquinoline can be further diversified by using known organopalladium reaction, such as Heck reaction, Suzuki cross-couplings and Sonogashira.[17] We next examined the reaction of the sensitive chloroketone, which also gave the corresponding quinoline in excellent yields (Table 2, entries 10 and 23), and no significant substituent effect was observed. Furthermore, the expected product can generate a diverse array of polysubstituted quinoline scaffolds.[18] Finally, in order to generalize the process, we used as the substrate 2-aminopyridine carboxaldehyde that was condensed with ketone, the overall yield is quite reasonable (Table 2, entries 29 and 30).[19] It is noteworthy that the reported procedure is an attractive methodology for the Friedländer synthesis of 1,8 naphthyridines with great efficiency.[20] However, R, R^3 and R^4 can be alkyl or aryl groups, and electron-donating or electron-withdrawing functionalities at different positions on the substrate were well tolerated and had no influence on the yield. As expected, the reaction was compatible with a wide scope of functional groups, and substituents, such as halo and methoxy, to provide the corresponding quinolines in excellent yields. Various substituted

Table 2 Friedländer synthesis of poly-substituted quinoline derivatives in the presence of T3P®



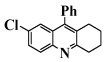
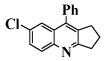
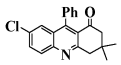
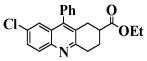
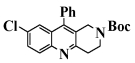
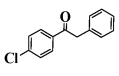
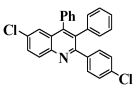
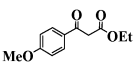
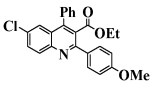
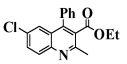
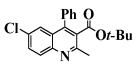
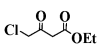
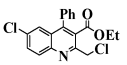
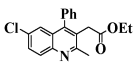
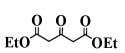
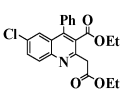
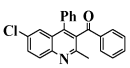
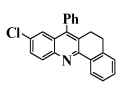
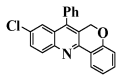
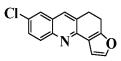
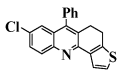
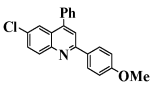
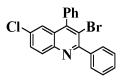
Entry	R	R^1	R^2	X	Ketone	Quinoline	Yield[a] (%)
1	Ph	H	Cl	CH			95
2	Ph	H	Cl	CH			90
3	Ph	H	Cl	CH			90
4	Ph	H	Cl	CH			93
5	Ph	H	Cl	CH			95
6	Ph	H	Cl	CH			94
7	Ph	H	Cl	CH			95
8	Ph	H	Cl	CH			93
9	Ph	H	Cl	CH			92
10	Ph	H	Cl	CH			90
11	Ph	H	Cl	CH			91
12	Ph	H	Cl	CH			91
13	Ph	H	Cl	CH			94
14	Ph	H	Cl	CH			96

Table 2 (*continued*)

Entry	R	R^1	R^2	X	Ketone	Quinoline	Yield[a] (%)
15	Ph	H	Cl	CH			95
16	Ph	H	Cl	CH			94
17	Ph	H	Cl	CH			93
18	Ph	H	Cl	CH			93
19	Ph	H	Cl	CH			96
20	Ph	H	Cl	CH			95
21	Me	H	H	CH			95
22	Me	H	H	CH			89
23	Me	H	H	CH			95
24	Me	H	H	CH			94
25	Me	H	H	CH			86
26	Me	H	H	CH			92
27	Me	MeO	MeO	CH			96
28	Me	MeO	MeO	CH			92
29	H	H	H	N			87
30	H	H	H	N			85

[a] Yields refer to isolated pure products.

2-aminoaryl ketones such as 2-amino-5-chloro-benzophenone and 2-aminonicotinaldehyde reacted smoothly with an appropriately substituted carbonyl derivative containing a reactive α-methylene group to produce a wide range of polysubstituted quinoline derivatives (Table 2, entries 6, 7, 14, 15, 19, 20, 29 and 30). In all cases, the results showed the excellent reactivity of T3P® under these conditions. The expected products were obtained with excellent purity and yields (85–96%) by recrystallization or precipitation and proved to be much better than those obtained using the classical methods reported in the literature. In general, the reaction is very clean, rapid and efficient.

In conclusion, we have introduced a highly efficient and robust method for the Friedländer annulation with T3P® under mild conditions. This method displayed high functional group tolerance and offers a simple and very efficient route for the synthesis of a wide range of polysubstituted, polycyclic quinolines and naphthyridines. This method avoids the use of hazardous acidic or basic reagents and harsh reaction conditions. The advantages of this protocol include short reaction times, excellent yields, simple work-up procedure, cost-effectiveness, environmentally eco-friendly benign and simple experimental operations. These advantages make this methodology attractive for large scale synthesis.[21] The access to other heterocycles by using T3P® is currently under investigation in our laboratory.

The authors are grateful to the institutions that supported their laboratory (Inserm, Université de Lille2, Institut Pasteur de Lille, USTL).

Experimental

General procedure for Friedländer reaction promoted by propylphosphonic anhydride (T3P®)

To a mixture of 2-aminoaryl ketone (0.5 mmol) and ketone (0.5 mmol) was added T3P® (50% in EtOAc) (0.5 mmol) in drops. The mixture was heated to 60 °C without added solvent for 0.5–1 h under air. After completion of the reaction (monitored by LC-MS), water (3 ml) was added to the reaction mixture and was shaken to dissolve the T3P®. The crude product was easily purified and isolated by recrystallization from hot methanol (2 ml) for more purification to give the pure polysubstituted quinolines. In all cases, the resulting products were isolated in total purity, as determined by LC-MS, and afforded analytically pure products in excellent to good yields in 85–96% as a solid.

5,6-Dihydro-7-methylbenzo[*c*]acridine (24). Yield (115 mg, 94%); grey solid; mp = 92–94 °C; purity: 100%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.68 (d, J = 7.5 Hz, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.68 (dd, J = 9.6, 6.9 Hz, 1H), 7.53–7.38 (m, 3H), 7.28 (d, J = 7.5 Hz, 1H), 3.11–2.95 (m, 4H), 2.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.62 (Cq), 146.88 (Cq), 139.77 (Cq), 139.11 (Cq), 135.28 (Cq), 130.25, 129.49, 128.40 (Cq), 128.26, 127.76 (Cq), 127.61, 127.25, 126.48, 125.83, 123.68, 28.17, 25.35, 13.91; rt (LCMS) = 3.33 min (5 min, pH = 3.8); HRMS-ESI (m/z): $[M + H]^+$ calcd for $C_{18}H_{16}N$ 246.1283; found 246.1295.

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