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A facile Horner–Wadsworth–Emmons route to 2-quinolones

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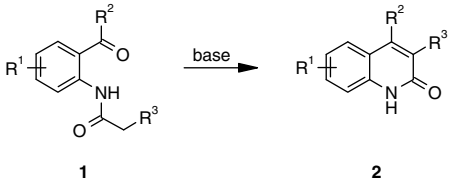
Abstract

2-Quinolones are prepared from *o*-aminophenylketones by N-acylation with phosphonoalkanoylchlorides, followed by an intramolecular Horner–Wadsworth–Emmons olefination. The transformation proceeds under mild conditions, is generally applicable, gives good yields and can be performed either in two steps or as a one-pot reaction.

Keywords: N-Heterocycles; 2-Quinolones; Cyclisation; Olefination

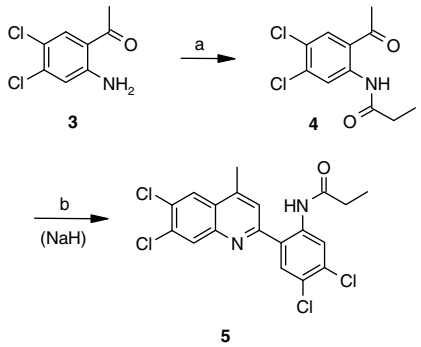
2-Quinolones (carbostyrils) are useful starting materials and form the core structures of a variety of bioactive substances.[1] Their preparation from anilines and β-ketoesters (Knorr synthesis) has been known for over 100 years;[2] numerous alternatives have since been developed.[3] A frequently employed method is an intramolecular condensation of an *N*-acyl-*o*-aminophenylketone **1** as outlined in Scheme 1. This reaction proceeds typically in high yields if either the carboxamide α-position is suitably activated (e.g., R^3 = ester,[4] aryl,[5] or pyridinium[6]) or the ketone motif in **1** withstands strongly basic conditions (e.g., if R^2 = aryl[3,7]). This method might, however, not be applicable if the acyl α-position is not activated, and if, at the same time, the ketone motif in **1** is readily enolised (e.g., if R^2 = R^3 = alkyl). For instance, **4** gave under the conditions of Park and Lee,[3] not a 2-quinolone, but quinoline **5** as a product of an intermolecular aldol condensation and imine formation in a low yield (Scheme 2).



1 **2**

Scheme 1. Quinolones **2** are frequently prepared from *N*-acyl-*o*-aminophenylketones **1**.

We found that this problem can be circumvented by acylating **3** with diethyl phosphonopropionylchloride (**7**-Me) to give **8**, followed by an intramolecular Horner–Wadsworth–Emmons (HWE) olefination (Scheme 3). Somewhat surprisingly, this rather obvious approach is unprecedented in the literature, although some methods to make quinolones involve intermediates similar to **8**: a



3 **4** **5**

Scheme 2. Compound **3** cannot be transformed into a quinolone according to Scheme 1. Reagents and conditions: (a) EtCOCl, Et_3N, CH_2Cl_2, rt weekend, 83%; (b) NaH (6 equiv), THF, 20 h reflux, 15%.

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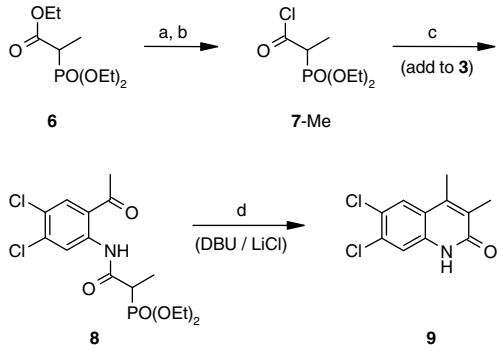
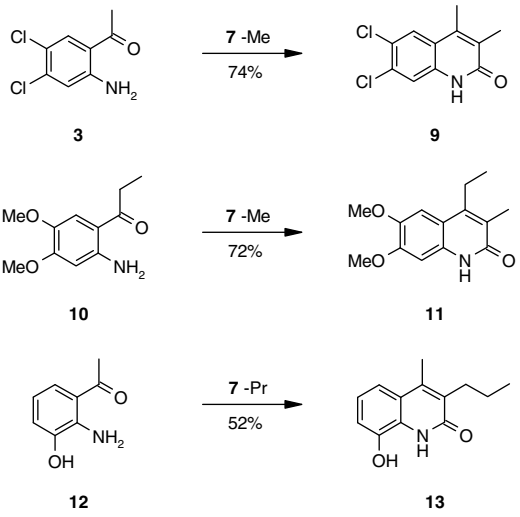


Scheme 3. Compound **3** can be transformed into quinolone **9** by acylation with **7**-Me, followed by an intramolecular olefination. Reagents and conditions: (a) KOH, EtOH, H_2O, 16 h rt, 90%; (b) $(ClCO)_2$, DMF, CH_2Cl_2, 6 h rt, quant.; (c) add to **3**, CH_2Cl_2, 0 °C to rt, 2 h, 82%; (d) DBU, LiCl, THF, 2 h rt, 86%.



Scheme 4. One-pot reactions exploring the scope of the acylation–olefination sequence. Typical reaction conditions: add **7**-Me to **3**, DBU (5 equiv), THF, 0 °C to rt, 6 h, then LiCl, rt overnight.

phosphonate ketene reagent was used to prepare *N*-methyl-phenylquinolin-2-one.[8] Carbamoylmethylphosphonates were transformed into 2-quinolon-3-yl phosphonates in a Knoevenagel-type condensation.[9] The possibility of a HWE olefination was mentioned in this Letter, but was not demonstrated. In another instance, a 2-quinolone was prepared in a low yield by a HWE reaction with concomitant amide formation.[10] The latter method had the disadvantage that it gave rise to the *trans*-olefin as the major product, which did not undergo cyclisation. 3-Unsubstituted 2-quinolones have been obtained in intramolecular Wittig reactions, either by the addition of an *o*-aminophenylketone to the Bestmann ylide, $Ph_3P{=}C{=}C{=}O$[11,12] or from a phosphonium salt with NaH as a base.[13]

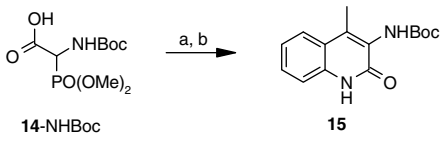
We obtained phosphonopropionylchloride **7**-Me from commercial **6** in two steps under standard conditions in high yields. The acylation of aminophenylketone **3** with this reagent led to **8**. When subjected to the mildly basic Masamune–Roush conditions (LiCl/DBU),[14] this intermediate underwent an intramolecular HWE olefination to give quinolone **9** in high overall yield (71% from **3**).

To investigate if this acylation–olefination sequence can also be performed as a one-pot reaction, we carried out the initial acylation step in THF as a solvent, using an excess of DBU as a base to trap liberated HCl (Scheme 4). After the near-complete consumption of **3** (~6 h), LiCl was added. Upon completion of the reaction, quinolone **9** was isolated in a yield comparable to the two-step process. During this and similar reactions, we found that 5 equiv of DBU are necessary for the olefination step in the one-pot setting.

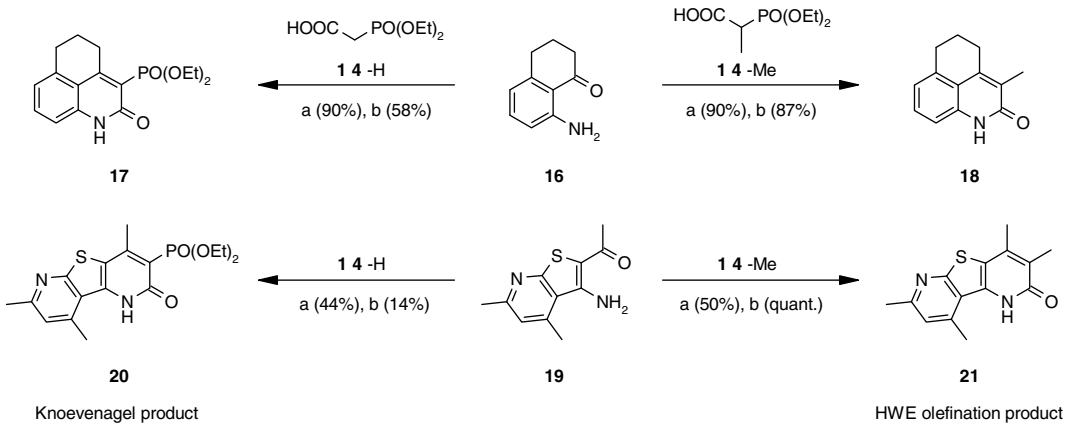
To explore if this method is equally applicable to electron-rich aminophenylketones, we converted **10** and the unprotected phenolic compound **12** with phosphonopropionylchloride **7**-Me or phosphonopentanoylchloride **7**-Pr into the corresponding 2-quinolones (Scheme 4). **7**-Me and **7**-Pr were used in amounts that were necessary for a complete acylation of the aminoketone starting materials (~1.5 equiv). Compound **11** was obtained in good yields, whereas **13** was isolated in a somewhat lower yield, possibly due to the reactivity of the free OH group and the formation of by-products with the excess of acid chloride reagent.

The acid-sensitive **14**-NHBoc[15] was transformed into quinolone **15** in two steps, using EDC as a condensation agent for the initial amide formation (Scheme 5). We observed that both EDC and **14**-NHBoc, which are water soluble and therefore easily removed during workup, are best used in a 2-fold excess for a complete conversion of the aminoketone starting material. The amide intermediate (not shown) then gave the desired 2-quinolone **15** in good yields.

Piperidine has been used as a base to prepare 2-quinolone-3-phosphonic acids from unsubstituted phosphonoacetylchlorides as a result of an intramolecular Knoevenagel condensation.[9] This prompted us to test if a Knoevenagel pathway might be preferred over the desired HWE olefination pathway with unsubstituted HWE reagents under the Masamune–Roush conditions. Indeed, when we transformed aminoketone **16** into a quinolone using the unsubstituted HWE reagent **14**-H,[16] we isolated exclusively the Knoevenagel product **17** (Scheme 6). For comparison, the methyl-substituted **14**-Me[16] cannot lead to a Knoevenagel reaction and formed, under the same conditions, the HWE olefination product **18** as expected. Analogously, the heterocyclic aminoketone **19** reacted with **14**-H to give the Knoevenagel product **20**, whereas with



Scheme 5. An EDC-mediated amide condensation was used to obtain quinolone **15** from the acid-sensitive **14**-NHBoc. Reagents and conditions: (a) *o*-aminoacetophenone (0.5 equiv), EDC, DMF, rt, overnight, 73%; (b) DBU, LiCl, THF, 4 h rt, 88%.



Scheme 6. Reagents and conditions: (a) **14** (2 equiv), EDC (2 equiv), DMF, rt, overnight, (b) DBU, LiCl, THF, 1 h rt. **19** was only partially converted in the initial amide-forming step despite an excess of reagents, which is the main reason for the relatively low yields in step (a). The amide intermediates (omitted for clarity) were isolated and characterised in all the cases.

14-Me, the HWE olefination product **21** was formed. Thus, at least when using the Masamune–Roush conditions for the olefination step, this synthetic method seems to be limited to the preparation of 3-substituted quinolones.

In summary, this Letter describes a convenient method to prepare 2-quinolones from aminophenylketones under mild conditions, which complements existing methods. The transformation can be carried out in two steps or as a one-pot reaction. 2-Quinolones with electron-donating as well as –withdrawing substituents (**9**, **11**, **13**, **15**, and **18**) and a heterocyclic quinolone analogue (**21**) could be prepared in generally good yields. Experimental details for the preparation of **11** as a typical example can be found in Ref. 17. The method is limited to the use of α-substituted HWE reagents, as the α-unsubstituted phosphonate **14**-H gave rise to Knoevenagel-type products rather than HWE olefination products.

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17. Preparation of **11**: (a) Phosphonopropionyl chloride **7**-Me: A solution of KOH (5.48 g, 84 mmol) in EtOH (12.5 ml) and H_2O (5 ml) was added dropwise to triethyl 2-phosphonopropionate **6** (20.00 g, 84 mmol) and the mixture was stirred at rt over the weekend. The volatile EtOH was evaporated, and the aqueous mixture was extracted with Et_2O. The aqueous layer was separated, acidified with 6 N HCl (pH 1), saturated with NaCl, and extracted several times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4), filtered and evaporated. The crude phosphonocarboxylic acid (15.51 g, 88%) was chlorinated without further purification: Oxalylchloride (870 mg, 7 mmol) was added dropwise to a solution of the obtained acid (1.20 g, 6 mmol) in CH_2Cl_2 (8 ml) and DMF (0.4 ml), and the mixture was stirred for 5.5 h at rt. The solvent was evaporated under reduced pressure and the residue was kept under vacuum overnight to remove residual DMF. The product (1.3 g, quant.) was used in the next step without further purification. (b) 4-Ethyl-6,7-dimethoxy-3-methyl-2-quinolone (**11**): DBU (1.09 g, 7.17 mmol) and phosphonopropionyl chloride **7**-Me (490 mg, 2.15 mmol) were added dropwise to a solution of *o*-aminophenylketone **10** (300 mg, 1.43 mmol) in THF (8 ml). After stirring overnight at rt, HPLC monitoring indicated the completion of the acetylation step. LiCl (91 mg, 2.1 mmol) was added and the mixture was stirred for an additional 4.5 h, after which HPLC analysis indicated the completion of the olefination step. The volatiles were evaporated, the residue was taken up in ethyl acetate, and washed with HCl (1 N) and satd $NaHCO_3$. After drying (Na_2SO_4) and evaporation of the solvent, the title compound (254 mg, 72%) was isolated from the residue by column chromatography (silica gel, CH_2Cl_2/MeOH = 100:0–90:10). ^{1}H NMR (DMSO-d_6): δ 1.14 (3H, t), 2.08 (3H, s), 2.84 (2H, q), 3.79 (3H, s), 3.82 (3H, s), 6.86 (1H, s), 7.12 (1H, s), 11.48 (1H, br s).