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An Efficient Synthesis Of Quinolones Using *N*-Phenyl(triphenylphosphoranylidene)ethenimine

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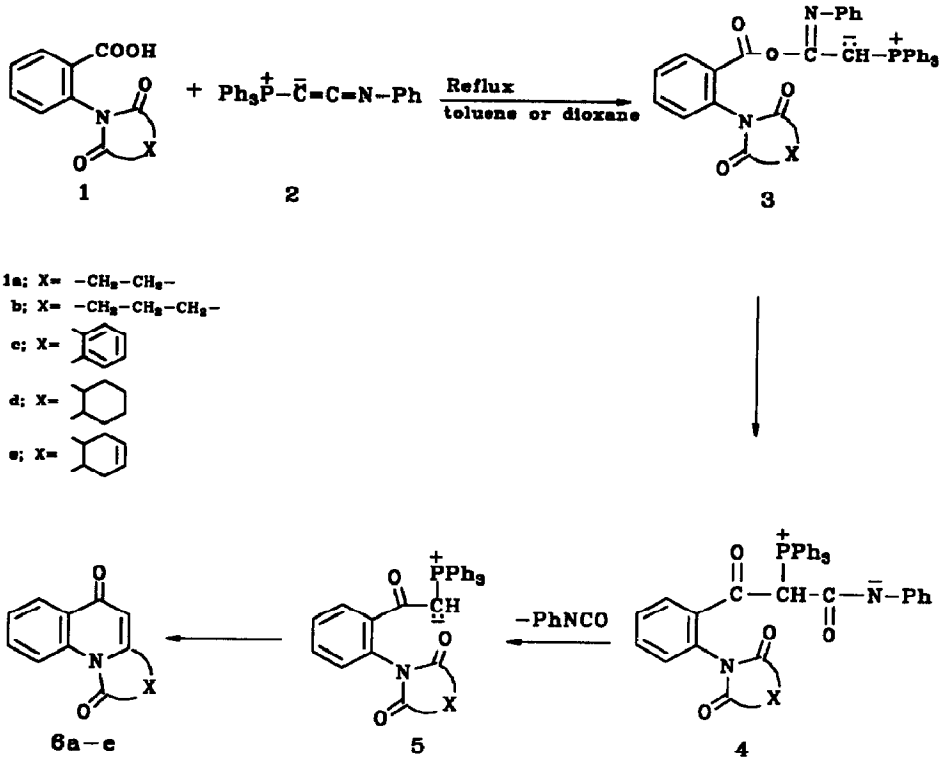
Abstract: *The acylphosphoranes* **5** *formed in a highly selective and sequential manner from the reaction of N-substituted anthranilic acids* **1** *and N-phenyl(triphenylphosphoranylidene)ethenimine* **2** *undergo intramolecular Wittig cyclization on the imide carbonyl to afford the pyrrolo- and pyrido[1,2-a]quinolones* **6** *in moderate to good yields.*

Quinoline compounds are endowed with an array of biological activities.[1] The last few years have witnessed considerable resurgence of interest for the synthesis and biological evaluation of quinolone antibiotics.[2] While a variety of synthetic methodologies for quinoline ring system have been developed,[3] the literature describing novel one-pot cyclization method based on consecutive processes is rather scarce. Here we report the successful use of *N*-phenyl(triphenylphosphoranylidene)ethenimine which led to an efficient synthesis of biologically relevant quinolones. The generality of this concept has been established with several models.

The synthesis of various imides **1a-e** was achieved by heating anthranilic acid with suitable anhydrides as per lit. procedure.[4] When a mixture of compound **1** and *N*-phenyl(triphenylphosphoranylidene)ethenimine[5] **2** was heated in refluxing toluene or dioxane, the desired quinolones[6] **6** were obtained in 45-97% yields. The conversion of **1** into **6** could be explained by a sequence of reaction as depicted in Scheme. The plausible mechanism can be visualized as initial protonation of *N*-phenyl(triphenylphosphoranylidene)ethenimine **2** by **1** followed by nucleophilic attack of the carboxylate ion to the resulting vinylphosphonium salt leading to *O*-acyl-imidate **3**. There is then a migration of the ester carbonyl from O to C[7] forming **4** followed by extrusion of phenyl isocyanate and ultimately leading to the acylphosphorane **5** which subsequently undergoes ring closure via the intramolecular Wittig reaction on the imide carbonyl to afford the desired quinolone.

Scheme



To support our suggested mechanism, the intermediacy of compound **4** has been established by chemical and spectroscopic means. Thus, the treatment of *N*-phthaloylanthranilic acid **1c** with **2** in toluene at room temperature gave the phosphorane **4c** which was isolated and characterized by satisfactory IR, ^{1}H-NMR and MS spectroscopic data.[6] Compound **4c**, on heating in refluxing toluene furnished the desired product **6c**.

Table: Synthesis of various quinolones **6** from **1** and **2** via intramolecular Wittig cyclization.

Entry	Reaction time(h)	Products[a]	Yield (%)[d]
1	6[b]	**6a**	97
2	6[c]	**6b**	45
3	8[b]	**6c**	70
4	6[b]	**6d**	60
5	6[c]	**6e**	55

[a] Products were characterized by satisfactory IR, ^{1}H NMR, ^{13}C NMR and MS spectra.[6] The spectroscopic data for compound **6a** and **6c** were in full agreement with the literature data.[8] [b] Reaction performed in toluene; [c] Reaction carried out in dioxane since the starting compound **1b** and **1e** were not sufficiently soluble in toluene; [d] Products were purified by silica gel column chromatography using pet. ether : ethyl acetate 80 : 20 as eluent. For purification of **6c**, pet. ether : ethyl acetate 90 : 10 was used as eluent. Yields refer to isolated pure products.

As is apparent from Table, the intramolecular Wittig cyclization involving phosphorous ylide and imide carbonyl is general for the preparation of a variety of quinolone derivatives. However, our initial attempt of intramolecular Wittig cyclization involving an amide carbonyl was a failure. Thus, the reaction of *N*-acyl(aroyl)anthranilic acids with **2** furnished the corresponding stable phosphoranes which failed to cyclize even under drastic reaction conditions. This could perhaps be attributed to the low reactivity of amide carbonyl whereas use of imide **1** facilitates the intramolecular Wittig cyclization due to enhanced electrophilicity which makes the carbonyl more reactive. Steric effect during Wittig cyclization resulting from *N*-substitution in **1** appears to be insignificant. Some of the synthesized compounds **6** can be converted into biologically useful 2-carboxyl-4-quinolone derivatives on treatment with a suitable base.[8] It is noteworthy that 2-carboxyl-4-quinolone derivatives exhibit anticonvulsant properties[9] and act as a potent and selective antagonists at the NMDA-glycine site. In this connection, the present methodology could be useful in designing a new and potent glycine-site *N*-methyl-*D*-aspartate receptor antagonists.[10]

In summary, an efficient methodology for a variety of quinolone derivatives has been developed. To our best knowledge, this is the first report of quinolone synthesis via intramolecular imide carbonyl olefination using *N*-phenyl(triphenylphosphoranylidene)ethenimine. We continue to explore the synthetic applications of novel phosphacumulene ylide.

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6. All compounds showed spectroscopic and analytical data in accordance with the structure. Spectroscopic data for selected compounds; **4c:** m.p. 178°C; IR νmax/cm^{-1} (Nujol) 1780, 1700, 1670, 1610, 1580, 1510; ^{1}H-NMR(200 MHz; $CDCl_3$) δ 6.8-8.05 (m, 28H), 12.4 (s, 1H); MS. m/z(%): 366 (M^+ - Ph_3P=O, 1%), 352 (4), 345 (15), 318 (31), 303 (100), 277 (84), 262 (5), 199 (11), 183 (13), 152 (4), 118 (5), 93 (6), 77 (8); **6d:** m.p. 139°C; IR νmax/cm^{-1} ($CHCl_3$), 3040, 2980, 2880, 1780, 1650, 1620, 1580, 1490, 1460, 1430; ^{1}H NMR(200 MHz; $CDCl_3$) δ 1.48 (m, 4H), 1.93 (m, 4H), 3.0 (m, 2H), 3.35 (m, 2H), 6.25 (s, 1H), 7.5 (m, 1H), 7.7 (m, 1H), 8.35 (dd, 1H, J=7.6, 1.8 Hz), 9.05 (d, 1H, *J*=8.8 Hz); ^{13}C NMR($CDCl_3$) δ 22.38, 22.49, 23.51, 29.22, 36.30, 41.78, 108.14, 118.18, 125.69, 126.33, 126.63, 133.34, 137.16, 158.63, 176.99, 179.55; MS. m/z: 253 (M^+).

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