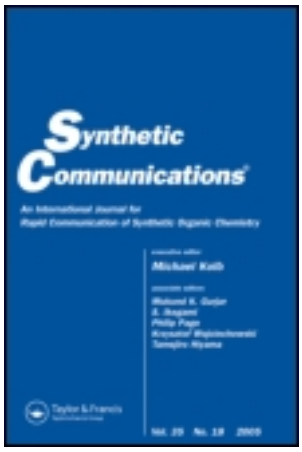

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Microwave Assisted Aza-Wittig Reactions of N-Imidoyliminophosphorane with Aldehydes: A Convenient and Selective Route to Quinazolines

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ABSTRACT

A novel synthetic strategy for the selective synthesis of biologically important quinazolines with shorter reaction times, better yields, lower energy inputs and hassle free work up using a domestic microwave oven is reported.

Key Words: Aza-Wittig; Microwave; N-Imidoyliminophosphoranes; Quinazolines.

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Phosphazenes[1] represent an important class of compounds and play a significant role in modern armoury of organic synthesis. These organophosphorus compounds have attracted a great deal of attention in recent years because of their broad range of application in the construction of carbon-nitrogen double bonds,[2–4] synthesis of azadienes[5–7] and heterocumulene associated azadienes.[8,9] Their utility in the preparation of various heterocycles including pyridine derivatives,[10,11] polycyclic compounds,[12] benzodiazepines[13] and pharmacologically active alkaloids[14] has also been well documented. However the reports on aza-Wittig reactions of N-imidoyliminophosphoranes are very rare.[15–18] Rossi et al.[15–17] have reported that the reactions of N-imidoyliminophosphoranes with various aldehydes resulted in a mixture of quinazoline and dihydroquinazoline derivatives in a ratio which was found to depend upon the nature of aldehydes as well as the employed thermal conditions. The reaction apparently suffers from disadvantages such as longer reaction periods (25–90 hrs), lower yields, lack of selectivity often leading to a mixture of products and cumbersome workup procedure.

Quinazolines being biologically and medicinally potent neoplasm inhibitors,[11] diuretics,[20] antimalarials,[21] antithrombics[22] and anticoagulants,[23] the development of a simple non-conventional route for their synthesis in improved yields was considered to be of immense significance. In recent years microwave heating[24] together with high pressure[25] and ultrasound[26] have been reported as important non-conventional techniques for accelerating the reaction rates and improving yields.[27,28] Seijas et al. have also reported the enhanced synthesis of quinazoline derivatives using microwave radiations.[29] Because of these potential advantages, we report herein a simple and convenient version of the aza-Wittig reaction of N-imidoyliminophosphoranes with aldehydes using a domestic microwave oven. Several experiments were performed at various power levels in order to establish the optimum reaction conditions. In a typical experiment, N-imidoyliminophosphorane **1** was mixed with 1.5 equivalents of aldehyde **2** and the mixture was exposed to microwave radiation at a power of 300 watts for a period of 3–4 minutes. The purification of the reaction mixture by flash chromatography resulted in the exclusive isolation of quinazolines **3** in good yields (65–80%) (Sch. 1).[21] Interestingly, the formation of dihydroquinazoline derivatives was not observed even in aza-Wittig reactions of **1** with para substituted aromatic aldehydes possessing strong electron donating groups viz. $-OCH_3$ and $-N(CH_3)_2$. This is in contrast to the earlier reports wherein the formation of dihydroquinazoline and their aromatisation was shown to depend on electronic factors. The observed absence of dihydroquinazolines in the present case suggests that the thermal conditions also play a predominant role in aromatisation of dihydroquinazolines to quinazolines. In conclusion, a

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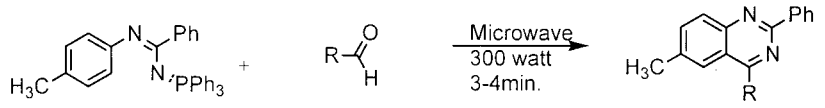

1 2 3

a. R=C_6H_5 (63%)
b. R=p-(NO_2)-C_6H_4 (72%)
c. R=p-(OMe)-C_6H_4 (77%)
d. R=p-(NMe_2)-C_6H_4 (73%)
e. R=p-(Cl)-C_6H_4 (67%)
f. R=C_6H_5-CH=CH (65%)

Scheme 1.

very simple, convenient, accelerated, less expensive and high yielding method for the selective synthesis of quinazolines is reported and further work is in progress.

6-Methyl-2,4-diphenylquinazoline (3a). Yield-72%, m.p. −266–227°C; 2.58 (s, 3H, $-CH_3$); 7.34–7.81(m, 11H, ArH); 8.01–8.05(d, 2H, ArH): δ_c (50.4 MHz) 21.5, 112.5, 118.0, 119.2, 124.0, 125.7, 127.2, 128.0, 128.5, 129.0, 130.1, 134.0, 137.8, 138.2, 144.8, 161.4, 162.8 m/z-296 (M^+).

6-Methyl-4-(4′-nitrophenyl)-2-phenylquinazoline (3b). Yield-73%, m.p. −189–190°C δ_H (200 MHz): 2.58 (s, 3H, $-CH_3$); 7.50–7.53 (m, 3H, ArH); 7.74–7.78 (d, 2H, $J = 8.0$ Hz, ArH); 8.02–8.08 (m, 3H, ArH); 8.44–8.48 (d, 2H, $J = 8.1$ Hz, ArH); 8.61–8.66 (m, 2H, ArH); δ_c (50.4 MHz) 21.9, 121.2, 123.7, 124.2, 128.4, 128.5, 129.2, 130.4, 130.6, 131.0, 136.3, 137.7, 137.9, 143.9, 148.5, 159.5, 165.0 m/z-341 (M^+).

6-Methyl-4-(4′-methoxyphenyl)-2-phenylquinazoline (3c). Yield-77%, m.p. −160–161°C, δ_H (200 MHz): 2.51 (s, 3H, $-CH_3$); 3.92 (s, 3H, $-OCH_3$); 7.09–7.13 (d, 2H, $J = 8.7$ Hz, ArH); 7.46–7.54 (m, 3H, ArH); 7.66–7.71 (d, 1H, $J = 10.0$ Hz, ArH); 7.85–7.90 (m, 3H, ArH); 8.00–8.05 (d, 1H, $J = 10.2$ Hz, ArH) 8.64–8.68 (m, 2H, ArH): δ_c (50.4 MHz) 21.8, 55.3, 113.9, 115.5, 121.5, 123.9, 125.6, 126.6, 127.2, 128.4, 128.8, 130.1, 130.5, 135.4, 136.8, 150.6, 159.4, 160.9.m/z-326 (M^+).

6-Methyl-4-(4′-dimethy1aminophenyl)-2-phenylquinazoline (3d). Yield-78%, m.p. −213–215°C, δ_H (200 MHz): 2.56 (s, 3H, $-CH_3$); 3.14 (s, 6H, −N(CH3)2); 6.91–6.96 (d, 2H, $J = 10.0$ Hz, ArH); 7.52–7.55 (m, 3H, ArH); 7.74–7.79 (m, 1H, ArH); 7.90–7.95 (d, 2H, $J = 10.0$ Hz, ArH); 8.03–8.07 (m, 2H, ArH); 8.68–8.73(m, 2H, ArH); δ_c (50.4 MHz) 20.9, 44.0 ($-N(CH_3)_2$), 114.2, 116.7, 120.6, 124.0, 125.9, 127.0, 127.2, 128.0, 128.8, 130.0, 130.9, 135.9, 137.5, 144.5, 160.7, 161.8 m/z-339 (M^+).

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6-Methy1-4-(4′-chlorophenyl)-2-phenylquinazoline (3e). Yield-72%, m.p. −180–182°C, δ_H (200 MHz): 2.57 (s, 3H, $-CH_3$); 7.12–7.16 (d, 2H, $J = 8.2$ Hz, ArH); 7.42–7.46 (d, 2H, $J = 8.2$ Hz, ArH); 7.53–7.56 (m, 3H, ArH); 7.75–7.79 (m, 1H, ArH); 7.83–7.88 (d, 1H, $J = 10.0$ Hz, ArH); 7.89–7.93 (d, 1H, $J = 10.0$ Hz, ArH); 8.65–8.69 (m, 2H, ArH): δ_c (50.4 MHz) 21.2, 112.3, 117.7, 119.5, 123.8, 126.0, 127.2, 127.8, 128.1, 129.0, 129.7, 130.7, 133.8, 137.9, 144.0, 161.2, 162.5 m/z-330.5 (M^+).

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