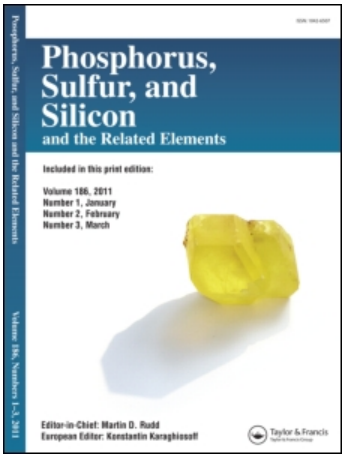

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A NOVEL SYNTHETIC APPROACH TO 4-SUBSTITUTED QUINAZOLINES

M. Srinivasan[a]; Jang Bahadur Rampal[a]
[a] Department of Chemistry, Indian Institute of Technology, Madras, India

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A NOVEL SYNTHETIC APPROACH TO 4-SUBSTITUTED QUINAZOLINES[1]

by

M. Srinivasan* and Jang Bahadur Rampal

Department of Chemistry, Indian Institute of Technology, Madras-600036, India

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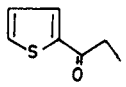
ABSTRACT

A novel two-step synthetic method to prepare 4-(thienyl)quinazolines (**8a** and **8b**) is described. The method is based on the simultaneous reductive cyclization of a nitro group β to the carbonyl group in ketones under Leuckart reaction conditions. The method has been found useful for the syntheses of the 4-substituted quinazolines.

The direct conversion of aldehydes and ketones to primary amines on heating with formamide/ammonium formate is the Leuckart reaction.[2] Recently it was shown that 2-propionylthiophene (**1**) with formamide gives thienyl substituted pyrimidines,[3] **2**, an anomalous Leuckart product in addition to the expected 1-(2-thienyl)-propylamine[4,5] **3**.



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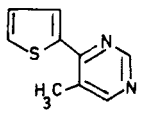

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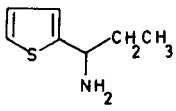
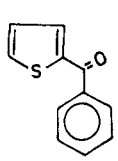


3

Unsubstituted benzoylthiophene,[6] **4**, gave the expected N-formyl derivative,[7] **5**, before deformylation, under Leuckart conditions, whereas 2-(*o*-nitrobenzoyl)thiophene (**6a**) gave a quinazoline derivative, **8a**, under a variety of conditions involving variation of the amount of ammonium formate as well as reaction temperature.[8]

From this it became obvious that the nitro group in such a position *viz.* β- to the carbonyl in ketones was also reduced and involved in a subsequent reaction. Formation of quinazoline under such conditions has not previously been reported and in fact nitrobenzene has been recommended as a solvent for this reaction.[2] Hence a detailed investigation, to confirm the reproducibility as well as to exploit the synthetic utility of the method was taken up with compound **6a** and its 3-methyl homolog **6b**.

These starting materials were prepared[9] as light yellow crystals in 55–58% yields by Friedel-Crafts



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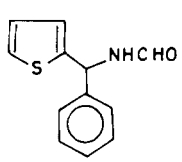

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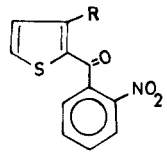
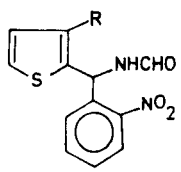


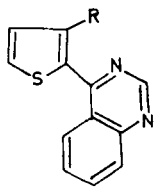
6a, R=H
6b, R=CH_3

acylation of thiophene or 3-methylthiophene with *o*-nitrobenzoyl chloride. The ketones were then subjected to conditions of the Leuckart reaction.

When **6a** and **6b** were heated with ammonium formate prepared from ammonia solution (28%) and formic acid (85% or 90%) or with formamide at 170°C, they failed to undergo the Leuckart reaction. However, when treated with ammonium formate obtained from 98% formic acid for 30 hr. at 195–205°, no starting materials were recovered and the products obtained showed neither the carbonyl absorption nor the NH absorption of the expected N-formyl compounds **7a** and **7b**.



7a, R=H
7b, R=CH_3



8a, R=H
8b, R=CH_3

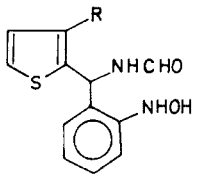
These compounds showed a sharp singlet at 9.2δ (one H) and 9.16δ (one H) respectively in 60 MHz

* To whom all correspondence should be sent.

nmr spectrum which could not be exchanged with D_2O. This low field proton, which could be confused for the > NHCHO proton, is also characteristic of the 2-proton of quinazoline. The uv absorption of the compounds was similar to the reported quinazoline absorption. Mass spectra and C, H analysis showed complete lack of oxygen in both the compounds. The formulas were $C_{12}H_8N_2S$ (**8a**) and $C_{13}H_{10}N_2S$ (**8b**). From all the above physical evidence it was concluded that the compounds must be 4-(2-thienyl)quinazoline (**8a**) and 4-(3-methyl-2-thienyl)quinazoline (**8b**).

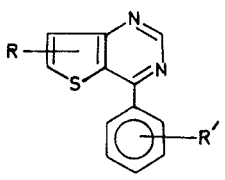
Literature survey showed compound **8a** to be identical with that reported by Otto Hans[10] which incidentally is a compound patented by Sandoz. This compound is anti-inflammatory, antipyretic and an analgesic.

So, for the quinazoline to have formed, the $-NO_2$ group of **6** should have been reduced to $-NHOH$ as in **9**, followed by dehydration and cyclization to **8**. If complete reduction of $-NO_2$ to $-NH_2$ had occurred, then a dihydro derivative of **8** would have resulted but this was not observed.



9a, R=H
9b, R=CH_3

When **8a** was refluxed with $POCl_3/PCl_5$ for 10 hr, a mixture of products resulted as indicated by tlc. On separation by chromatography, monochloro (36.5%), dichloro (21.4%), and trichloro (trace) derivatives were obtained. The Cl of the monochloro compound was thought to be substituted into the thiophene nucleus of **8**, based on spectral data. Tentative assignment of chlorines in the dichloro compound are one, at the thiophene ring and the other on C-2 of the quinazoline ring. The uv spectrum of the trichloro compound was similar to quinazoline and the mass spectrum was satisfactory for a trichloro derivative but too little was at hand for further study.



10

So to see the effect of $POCl_3$ alone, on **8a**, it was refluxed with $POCl_3$ and a compound mp 126°C resulted in fair yield as the sole product. From its mixed mp and spectral data it was found to be identical with the monochloro compound.

The new method above involves just two steps with high overall yield for the synthesis of thienylquinazoline and also would be useful for the syntheses of a number of thienylquinazolines as well as substituted thienopyrimidines, **10**. The method has since been applied to other systems and found to work equally well for the formation of 4-substituted quinazoline. Work is underway with nitro group in the thiophene ring as well as nitro group in position other than β– to the carbonyl and the results will be reported shortly.

Experimental Section

Melting points are in degrees centigrade determined in open capillary tubes in an electrically heated block apparatus and are uncorrected. A Perkin-Elmer Model 257 spectrophotometer was used to record all infrared spectra in the range 625–4000 cm^{-1}. Mass spectra were taken in a Varian CH-7 instrument. High resolution mass spectra were run at the University of Montreal by Prof. D. C. Dejongh. Nmr spectra were run in a Varian 60D instrument, $CDCl_3$ serving as solvent and TMS as internal standard. Uv was taken in Carl Zeiss DMR-21 model instrument.

2-(o-Nitrobenzoyl)-3-methylthiophene (**6b**)

A solution of 3-methylthiophene (4.9 ml, 0.05 mol) and *o*-nitrobenzoyl chloride (9.2 g, 0.05 mol) in dry carbon disulfide (40 ml) was added dropwise to a stirred suspension of aluminum chloride (8.6 g, 0.065 mol) in dry carbon disulfide (60 ml) maintained at 0°C during 45 min. The mixture was stirred at 10° for 1 hr after the addition was complete, then at 25° for 8 hr, and finally was refluxed for 2 hr, cooled and poured on to ice containing 30 ml of hydrochloric acid (1:1) and extracted with ether. The extract was washed with water, sodium carbonate solution and water and then dried ($MgSO_4$). The dark brown residue obtained on removal of ether was dissolved in benzene (30 ml) and decolorized with animal charcoal and filtered. Benzene was then removed to get a yellow mass which gave fine yellow needles from ethyl acetate: mp 100°, 6.98 g (55%), uv λ_{max} (MeOH) 202 nm (16860), 212 nm (15200), and 274 nm (18050), ir ($CHCl_3$) 1650 cm^{-1} (> C = O); nmr 2.43 δ(s, 3H); ms (M^+), m/e = 247.

Anal. Calc: for $C_{12}H_9NO_3S$: C, 58.30; H, 3.67.
Found: C, 58.62; H, 4.06.

4-(3-Methyl-2-thienyl)quinazoline (**8b**)

Aqueous ammonia (30%, 10 ml, 0.10 mol) was mixed with formic acid (98%, 9.8 ml, 0.21 mol) while cooling at 0°. The temperature was raised to 165–170° by distilling out water and 2-(*o*-nitrobenzoyl)-3-methylthiophene (**6b**)

1.23 g, 0.005 mol) was added in one portion. The temperature was maintained at 195–205° for 30 h, cooled, extracted with benzene and dried ($MgSO_4$). The benzene solution was decolorized with animal charcoal and filtered. The filtrate was evaporated *in vacuo* to give a solid residue, which was recrystallized from ligroin as very light yellow needles: mp 123°, 0.72 g (61%); uv (MeOH) λ_{max} 225 nm (31080), 285 nm (4689), 335 nm (8247); nmr 2.23 δ(s, 3H); 9.16 δ(s, 1H); ms (M^+) m/e = 226 $(M-1)^+$ m/e = 225 (base peak).

Anal. Calc: for $C_{13}H_{10}N_2S$: C, 69.01, H, 4.46.
Found: C, 69.25; H, 4.57.

4-(2-Thienyl)quinazoline (8a)

2-(*o*-Nitrobenzoyl)thiophene (6a) (2.33 g, 0.01 mol) was added in one lot to ammonium formate (10 ml, 0.20 mol) and heated at 195°–205° for 50 hr. It was then worked up as before to yield the 4-(2-thienyl)quinazoline (8a) which was recrystallized from ligroin as white crystalline needles, mp 65° (lit[9] 66°) yield 1.79 g (80%); uv λ_{max} (MeOH): 229 nm (10970), 301 nm (6184), 341 nm (11760); nmr 9.2 δ(s, 1H); ms (M^+) m/e = 212, $(M-1)^+$ m/e 211 (base peak).

Anal. Calc: for $C_{12}H_8N_2S$: C, 67.92; H, 3.77.
Found: C, 68.18; H, 4.02.

Reaction of 8a *with phosphorus oxychloride/phosphorus pentachloride:*

4-(2-Thienyl)quinazoline (8a) (2.12 g, 0.01 mol) was dissolved in phosphorus oxychloride (10 ml) and phosphorus pentachloride (1 g) was then added to it. The solution was refluxed for 10 hr, then cooled and decomposed with ice. The aqueous layer was separated, washed with benzene, made basic with ammonia (28%), extracted with benzene, dried ($MgSO_4$) and solvent removed. The TLC of the product (crude) showed two major spots and one minor spot. It was dissolved in minimum amount of chloroform and chromatographed over alumina column. Elution with benzene gave a very small amount of a material mp 182° which was indicated to be a trichloro compound by its mass spectrum.
ms (M^+) m/e = 314.

Continued elution with benzene-chloroform (1:1), gave 0.6 g (21.4%) of a compound mp 164° (ligroin), with uv λ_{max} (MeOH), 238 nm (5247), 310 nm (1756), 359 nm (3880); nmr no low field proton was observed:
ms (M^+) m/e = 280.

Anal. Calc: for $C_{12}H_6Cl_2N_2S$; C, 51.27; H, 2.15; N, 9.97.
Found: C, 50.94; H, 2.19; N, 9.87.

Further elution with chloroform gave a total of 0.9 g (36.5%) very light yellow crystalline material. After two recrystallizations from carbon tetrachloride/ligroin the sample had mp 126° and from analysis and ms, it was found to be a monochloro compound uv λ_{max} (MeOH), 220 nm (8814), 272 nm (1595), 345 nm, (1609), nmr 9.16 δ(s, 1H) ms (M^+) m/e 246.

Anal. Calc: for $C_{12}H_7ClN_2S$: C, 58.53 H, 2.84.
Found C, 58.50 H, 2.79.

Reaction of 8a *with phosphorus oxychloride:*

The above experiment was repeated with only phosphorus oxychloride (5 ml) and 8a (1.06 g, 0.005 mol), refluxed for 6 hr and worked up as mentioned above to get a yellow crystalline material, recrystallized from carbon tetrachloride/ligroin, mp 126°, as the sole product. This was found identical with the monochloro compound obtained in the previous reaction.

Acknowledgment

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