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Expeditious Routes to 4-Alkoxyquinazoline-2-carbonitriles and Thiocarbamates *via* *N*-Arylimino-1,2,3-dithiazoles Using Microwave Irradiation[1]

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Abstract: Conversion of *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazole **11** into the 4-alkoxyquinazoline-2-carbonitriles **13a-i** and of the aryl isothiocyanates **15** into aryl thiocarbamates **16a-j** with sodium alkoxides in the corresponding alcohol, either by conventional thermolysis or by microwave irradiation are described and directly compared. Microwave irradiation of the solutions in open vessels in a monomode system with focused irradiation and continuous temperature control (Synthewave S402 reactor) usually gave cleaner, faster and higher yielding reactions. These reactions could be safely and beneficially scaled up to multigram quantities in a larger reactor (Synthewave S1000).

Microwave irradiation is a powerful technique which is being increasingly used to accelerate thermal organic reactions. The earliest reported microwave-assisted organic reactions were carried out with commercial (multimode systems) or domestic ovens and rudimentary reaction vessels.[3] Although spectacular rate enhancements were described, there were hazards associated with microwave heating of organic reactions, including deformation of vessels and explosions. Whilst valuable, the technique was perceived as potentially dangerous owing to the flammability of solvents; to retain its benefits and minimize the risks, "dry media" techniques have attracted much attention and have been developed in open ovens under atmospheric pressure (multimode or monomode systems).[4]

Whilst studying the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride **1** and its derivatives,[5] we have transposed many of the reactions to a focused microwave oven (open oven, monomode system) especially designed for organic synthesis, with the aim of achieving striking reductions in reaction times, better yields and cleaner reactions than for the purely thermal processes. In this paper we describe new routes to 2-cyanoquinazolines and thiocarbamates *via* 1,2,3-dithiazolium derivatives. Conventional heating and microwave irradiation of the reactions are reported and compared. Studying the potential effect of the homogeneity of the starting mixture on the yield and reaction time, we decided to extend the scale of our procedures in an oven allowing irradiation of solutions of 800 ml in mild and safe conditions.

4,5-Dichloro-1,2,3-dithiazolium chloride **1**,[6] which is readily prepared from chloroacetonitrile and disulfur dichloride, reacts rapidly with anilines in dichloromethane at room temperature to give the stable *N*-arylimino-4-chloro-5*H*-1,2,3-dithiazoles **2** usually in high yield.[5-12] These iminodithiazoles have electrophilic centres at S1, S2, C4 and C5, and are susceptible to intramolecular (*e.g.* **3**) and intermolecular (*e.g.* **4**) nucleophilic substitution at both sulfur and both carbon atoms of the dithiazole ring and, in consequence, have proved to be very versatile synthetic intermediates. They can be converted in one step into the 2-cyano derivatives of benzoxazoles **5**,[7] benzothiazoles **6**,[8,9] benzimidazoles **7**,[10] benzoxazines **8**,[11,12] benzothiazines **9**,[11,12] and into the acyclic *N*-arylcyanothioformamides **10**.[9]

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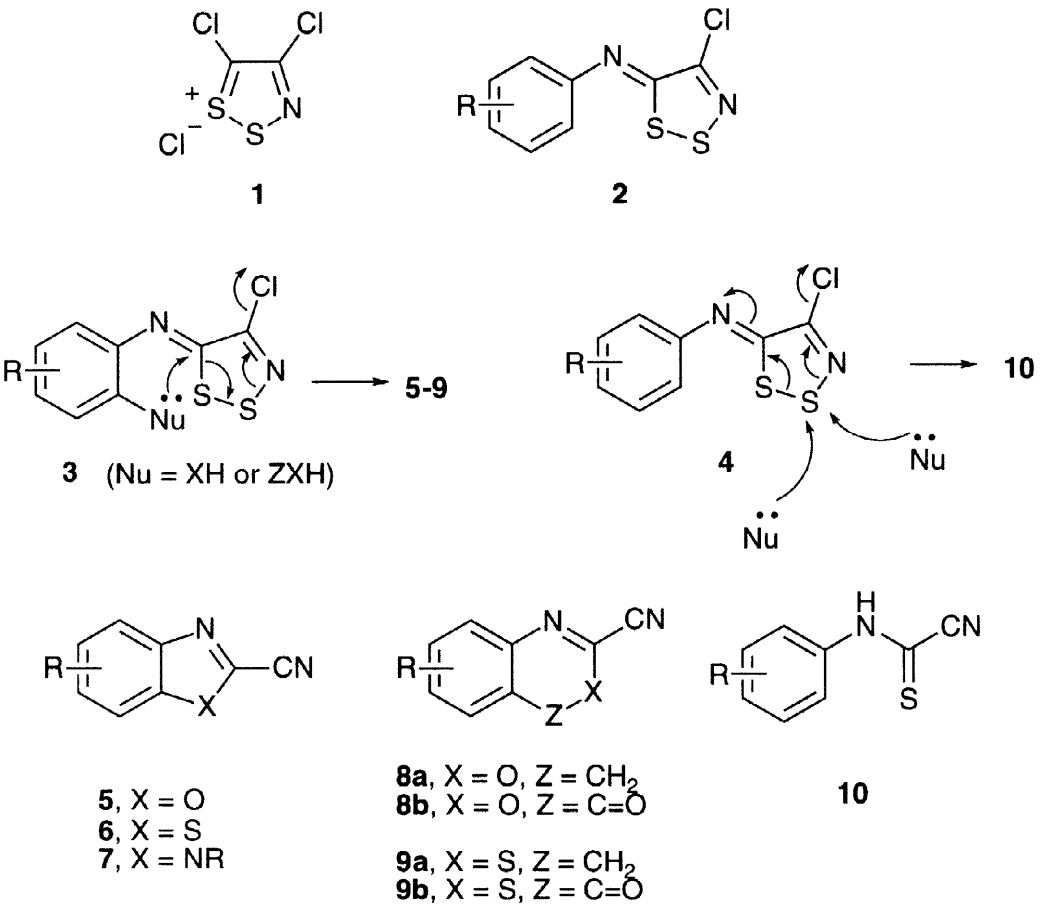
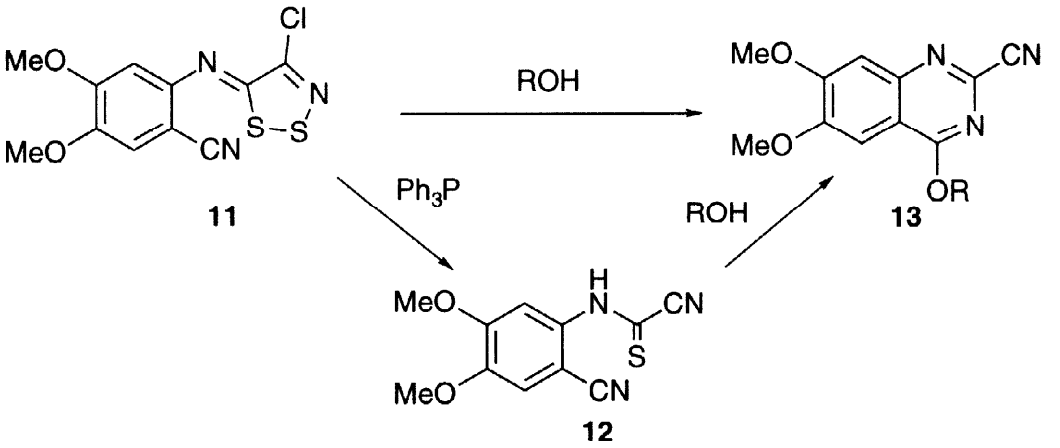


Scheme 1

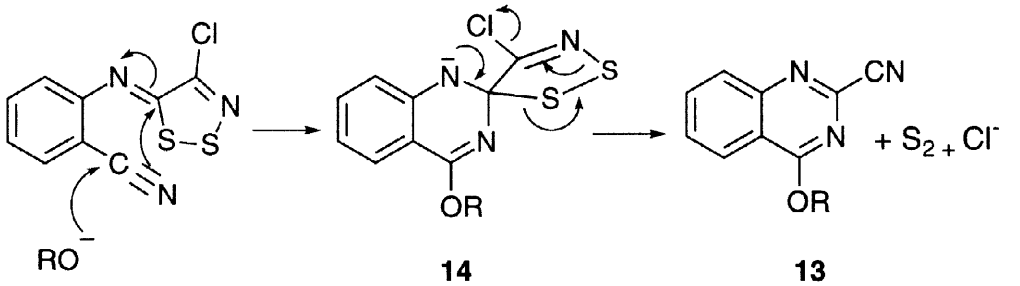
Synthesis of 4-alkoxyquinazoline-2-carbonitriles

Recently we have shown that introduction of a cyano group into the *ortho* position of the *N*-aryl group of the imines **2** allowed formation of novel 4-alkoxyquinazolines **13**,[5a] derivatives of which continue to be of interest because of their diverse biological activity [*e.g.* potent alternate inhibitors of human leucocyte elastase, herpes simplex (HSV-1) and C1 complex (C1r) serine proteases and porcine cyclic GMP phosphodiesterase].[13] We also found that with triphenylphosphine (2 equiv.) in moist dichloromethane at room temperature imine **11** gave the cyanothioformamide **12** which was separated from the reaction mixture but was not very stable. Attempted recrystallization of this product from ethanol was accompanied by the characteristic odour of hydrogen sulfide and afforded a blue (UV) fluorescent product purified by chromatography and characterized as 4-ethoxy-6,7-dimethoxyquinazoline-2-carbonitrile **13** (R = Et).[5a] The *N*-arylimino-1,2,3-dithiazole **11** is considerably more stable than the derived cyanothioformamide **12** but it did react slowly with alcohols to give quinazoline-2-carbonitriles **13**. Long heating of the imine in alcohols at reflux (5 days) gave the corresponding quinazolines **13** in low to modest yields. The yields were increased and the time of the reaction reduced (5 days → 40 h) when the alcohol was first treated with one equivalent of sodium hydride (Table 1).

A reasonable mechanism (Scheme 3) would appear to be addition of the alkoxide ion to the cyano group and cyclisation to give the spiro intermediate, **14**, or its *N*-protonated form, which could rapidly fragment to give the aromatic 2-cyanoquinazoline, together with disulfur and chloride ion.



Scheme 2



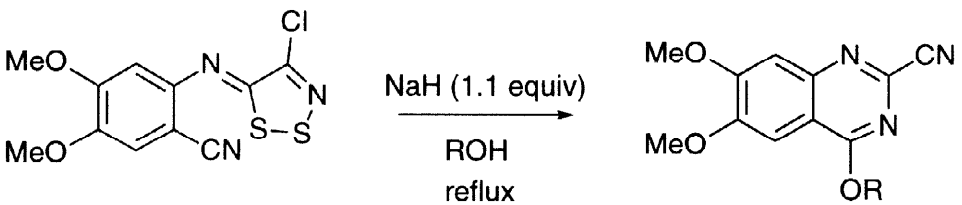
Scheme 3

The yields of the quinazolines **13** may be improved in a shorter reaction time (2 h) by microwave irradiation of the reaction mixture, which was cleaner (no by-products detected) than under classical heating. The results, presented in Table 1, are in agreement with many recent reports of faster and cleaner synthetic reactions under microwave irradiation, compared to conventional heating.[4] Bases which deprotonate the alcohol gave a substantial reduction in reaction time with sodium hydride being the reagent of choice. Without any base a decrease of the reaction time was observed in the presence of $AgNO_3$, suggesting that ionisation of the chlorine can be the rate-limiting step of the process.[14]

The open microwave reactors used in these experiments were especially designed for organic synthesis. The Synthewave™ S402 (Prolabo, monomode system) has quartz reactors, variable speed rotation, visual control, focused irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC).[15] Many thermal reactions performed in the presence of solvent may also be realised with this system, but one major problem is the capacity of the quartz reactors used which is limited to 70 ml. We observed that it was not possible to increase the quantity of the starting imine without also increasing the volume of the solvent. The ratio between the quantity of the material and the solvent was very important; if it is too large hazardous solvent bumping in the reactor may result.

We studied the influence of the concentration of the starting imine **11** on the reaction time and yield in the formation of the *n*-butoxyquinazoline **13e** under microwave experiments. The results are shown in Table 2; experiments were performed with *n*-butanol as the solvent. We observed that the best results were obtained with a concentration of 3% of the starting iminodithiazole **11** where the yield reached 71% in the optimum reaction time (35 min). A larger quantity of the imine (*e.g.* 20%) involved a reduction in reaction time (15 min) with a good yield of 67%; this mixture was not a clear solution but a heavy syrup or gum which made the work-up less

attractive. The reaction conditions defined in the Synthewave™ S402 microwave reactor were transposed to another open microwave oven (Synthewave™ S1000) which has an enlarged capacity for reactions in the presence of solvents (from 100 to 800 ml). We observed (Table 2) that this transposition allowed a ready production of our compounds in yields comparable to those obtained in the smaller reactor. The time of the reaction was also reduced, probably due to the higher power capacity of the second reactor (800W for the S1000 oven instead of 300W for the S402).



11 **13**

Table 1. Preparation of quinazolines **13** from the imine **11**

R	Product **13**	Conventional heating [a]		Microwave irradiation	
		reaction time	yield (%)	reaction time	yield (%)
Me	**a**	40 h	77	2h	n.r.[c]
Me	**a**	40 h	76	2 h	41[b]
Et	**b**	40 h	77	2 h	80
Et	**b**	40 h	29	2 h	80 [b]
n-Pr	**c**	40 h	39	73 min	49
i-Pr	**d**	40 h	63	2 h	n.r.[c]
n-Bu	**e**	40 h	82	35 min	70
t-Bu	**f**	40 h	n.r.[c]	2 h	n.r.[c]
n-C_5H_{11}	**g**	40 h	57	35 min	63
CH_2=CH-CH_2	**h**	40 h	60	35 min	69
$(CH_3)_2CH(CH_2)_2$	**i**	40 h	31	45 min	31

[a] : Oil bath; [b] : H instead of the OMe groups in the benzene ring; [c] n.r. : no reaction

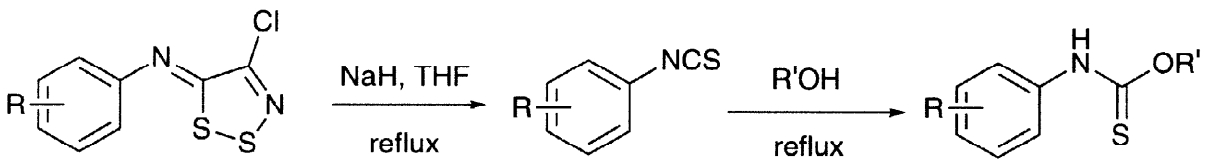
Table 2. Effect of the concentration of the starting imine **11** for the synthesis of 4-(*n*-butoxy)quinazoline **13e** under microwave irradiation

	Synthewave S402 (300W)		*Synthewave S1000 (800W)*	
Weight (g) of imine **11**[a]	time (min)	yield (%)[b]	time (min)	yield (%)[b]
1	120	66	70	60
3	35	71	26	68
5	35	65	-	-
7.5	20	60	-	-
10	20	55	-	-
20	15	67	-	-

[a] For 100 ml of solvent; [b] All the reactions were performed 3 times and the yields given are the average values.

Synthesis of thiocarbamates

Recently, during an investigation of the chemistry of arylimino-1,2,3-dithiazoles **2**, we discovered a new method for converting arylamines into aryl isothiocyanates **15** in good yields *via* the dithiazoles **2**.[16] Alcohols may be added to isothiocyanates to form aryl thiocarbamates **16**[17] which may be cyclised to 2-alkoxybenzothiazoles,[18] which are useful precursors of thiazole natural products. Because we were interested in producing larger quantities of thiocarbamates in clean and rapid reactions, we transposed the classical procedure to our microwave ovens. We first studied the reaction in the small scale reactor and then extended this to the larger one with attention focused on the influence of the concentration of the starting material on the behavior of the reaction (bumping, yield and reaction time).



2 **15** **16**

Scheme 4

In the classical process the isothiocyanates **15** were refluxed for 8-10 h in a large excess of the alcohol to afford the corresponding thiocarbamates **16** in good yields (65-80%). Alternatively, when the more strongly nucleophilic alkoxide anions were used, the reaction was complete in 1h in very good yields (80-98%). Transposing this procedure to the open focused microwave reactor (Synthewave S402) allowed a spectacular reduction in reaction time (Table 3) and also resulted in very good yields under safe conditions (no bumping of the reaction mixtures were detected). The reactions were cleaner than for the purely thermal method and the products more easily purified.

Table 3. Preparation of arylthiocarbamates **16** from aryl isothiocyanates **15** under microwave irradiation

Isothiocyanate **15** R	Product **16**	R'	time (min)[a]	yield of product (%)[a]
H	**a**	*n*-Bu	120 / 3	97 / 98
H	**b**	*n*-Pr	120 / 3	75 / 98
H	**c**	Et	240 / 3	71 / 98
2-CN	**d**	*n*-Bu	45 / 3	89 / 93
4-OMe	**e**	*n*-Bu	120 / 3	92 / 93
4-OMe	**f**	*n*-Pr	120 /3	60 / 80
4-CN	**g**	*n*-Bu	15 / 0.15	94 / 98
4-CN	**h**	*n*-Pr	20 / 0.5	95 / 98
2,5-diOMe	**i**	*n*-Bu	240 / 15	59 / 85
2,5-diOMe	**j**	*n*-Pr	120 / 15	48 / 83

[a] Time and yield of the reaction : without base / in the presence of base (1.1 equiv. of NaH or potassium *tert*-butoxide).

All the solutions irradiated in this procedure were homogeneous. We studied the influence of the concentration of the mixture on the reaction with phenyl isothiocyanate and *n*-butanol (Table 4). As described before for the synthesis of quinazoline **13e**, the reaction conditions defined in the smaller microwave oven were transposed to the Synthewave S1000 oven, allowing larger scale reactions. The yields were excellent in very

short times (3-5 min) and no hazards were detected, underlining the advantage of working with homogeneous solutions under microwave irradiation.

Table 4. Effect of the concentration of phenyl isothiocyanate **15a**[a] for the synthesis of carbamate **16a** under microwave irradiation

	Synthewave S402 (300W)		*Synthewave S1000 (800W)*	
Weight (g) of isothiocyanate[b]	time (min)	yield (%)[c]	time (min)	yield (%)[c]
1	4	95	5	89
3	3	98	-	-
5	3	98	-	-
10	3	92	3	86
15	2	97	-	-
20	2	88	3	84

[a] Commercially available; [b] For 100 ml of solvent; [c] All the reactions were performed 3 times and the yields given are the average values.

In conclusion, we have described a synthesis of the quinazoline ring from *N*-arylimino-1,2,3-dithiazoles by thermolysis and by microwave irradiation, and of the thiocarbamates from isothiocyanates, themselves generated from arylimino-1,2,3-dithiazoles. Our results provide further examples of the utility of microwaves in organic syntheses in the presence of solvents. New open focused microwave reactors such as the Synthewave S402 and S1000 minimize the risks of explosion and hazardous bumping previously experienced with multimode systems (domestic ovens). The reactions described here were extended to a larger scale without problems, allowing multigram production of useful heterocyclic intermediates.

EXPERIMENTAL

Mps were determined using a Kofler block and are uncorrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^{1}H and ^{13}C-NMR were recorded on a JEOL JNM LA400 (400 MHz) spectrometer (Laboratoire Commun d'Analyse, Université de La Rochelle); chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Coupling constants *J* are given in Hz. Mass spectra were recorded on a Varian MAT311 spectrometer in the Centre de Mesures Physiques de L'Ouest (C.R.M.P.O.), Université de Rennes. Chromatography was carried out on silica gel 60 at medium pressure and the reaction mixtures were applied to the column preadsorbed onto silica. Light petroleum refers to the fraction b.p. 40-60°C. Further solvents were used without purification. Thin-layer chromatography was performed on Merck Kieselgel 60 F254 aluminium backed plates.

Focused microwave irradiations were carried out with Synthewave™ S402 (capacity of the quartz reactor used: 10 and 70 ml) and Synthewave™ S1000 (solutions of 100 to 800 ml) Prolabo® microwave reactors (monomode system).[15]

Spectral data for compounds **11**, **13a**, **13b**, **13d** and **13e** are consistent with assigned structures, as previously described in ref. 5a .

4-Substituted-quinazoline-2-carbonitriles: general procedures

Method A: conventional heating. A stirred mixture of *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)-4,5-dimethoxyanthranilonitrile **11** (0.2 g, 0.64 mmol) and sodium hydride (NaH, 0.018 g, 0.77 mmol) in the alcohol (6.8 ml) was heated at reflux in an oil bath for 40 h. The hot solution obtained was filtered, the solvent evaporated and the product **13** was purified by column chromatography (dichloromethane-light petroleum).

Method B: microwave experiments. The same reaction mixture was placed in a microwave reactor (Synthewave™ S402 or S1000) in an open flask. The irradiation was programmed for 2 h with a delay of 10-15

seconds to obtain the reflux.The solution was irradiated until the starting imine had been used up (TLC) and the product purified as described above.

6,7-Dimethoxy-4-propoxy-quinazoline-2-carbonitrile 13c (R = *n*-C_3H_7) Colourless needles, mp 215°C (from petroleum ether) (Found: M^+, 273.1114. $C_{14}H_{15}N_3O_3$ requires *M*, 273.1113); ν_{max} (KBr)/cm^{-1} 2960, 2238 (CN), 1611, 1577, 1552, 1477, 1368, 761 and 737; δ_H(400 MHz, $CDCl_3$) 1.10 (3H, t, *J* 7.99, $CH_3CH_2CH_2O$), 1.94 (2H, sextuplet, *J* 7.2, $CH_3CH_2CH_2O$), 4.05 (3H, s, OMe), 4.55 (3H, s, OMe), 4.56 (2H, t, *J* 6.79, $CH_3CH_2CH_2$), 7.31 (1H, s, Har), 7.38 (1H, s, Har); δ_C(100 MHz, $CDCl_3$) 10.46, 22.06, 53.43, 56.44, 59.53, 69.63, 101.14, 107.12, 111.81, 116.45, 138.17, 148.03, 156.15, 165.56; *m/z* 273 (M^+, 39%), 244 (M^+ - [CH_3CH_2], 14), 231 (M^+ - [$CH_3CH{=}CH_2$], 100), 216 (M^+ - [$CH_3CH{=}CH_2$, CH_3], 25).

6,7-Dimethoxy-4-pentoxy-quinazoline-2-carbonitrile 13g (R = *n*-C_5H_{11}) Colourless needles, mp 134°C (from light petroleum) (Found: M^+, 301.1429. $C_{16}H_{19}N_3O_3$ requires *M*, 301.1426); ν_{max} (KBr)/cm^{-1} 3021, 2961, 2238 (CN), 1611, 1577, 1506, 1478, 1429, 1269, 1170 and 993; δ_H(400 MHz, $CDCl_3$) 0.94 (3H, t, *J* 7.0, $CH_3CH_2CH_2CH_2CH_2O$), 1.41-1.48 (4H, m, $CH_3CH_2CH_2CH_2CH_2O$), 1.89 (2H, t, *J* 7.0, $CH_3CH_2CH_2CH_2CH_2O$), 4.47 (2H, t, *J* 6.7, $CH_3CH_2CH_2CH_2CH_2O$), 4.02 (3H, s, OMe), 4.03 (3H, s, OMe), 7.28 (1H, s, Har), 7.35 (1H, s, Har); δ_C(100 MHz, $CDCl_3$) 13.98, 22.37, 28.09, 28.31, 56.42, 56.51, 68.27, 101.17, 107.14, 111.81, 116.62, 138.27, 148.03, 151.71, 156.15, 165.58; *m/z* 301 (M^+, 17%), 244 (M^+-[$CH_3CH_2CH_2CH_2$], 4), 231 (M^+-[$CH_2{=}CHCH_2CH_2CH_3$], 100).

6,7-Dimethoxy-4-(prop-2-enoxy)-quinazoline-2-carbonitrile 13h (R = $CH_2{=}CHCH_2$) Colourless needles, mp 205°C (from light petroleum) (Found: M^+, 271.0956. $C_{14}H_{13}N_3O_3$ requires *M*, 271.0957); ν_{max} (KBr)/cm^{-1} 3098, 2946, 2240 (CN), 1611, 1578, 1517, 1474, 1272, 1171 and 998; δ_H(400 MHz, $CDCl_3$) 4.02 (3H, s, OMe), 4.03 (3H, s, OMe), 5.09 (2H, d, *J* 6.1, $CH_2{=}CHCH_2O$), 5.36 (1H, dd, *J* 1.3 and 10.4, $CH_aH_b{=}CHCH_2O$) 5.48 (1H, dd, *J* 1.3 and 10.4, $CH_aH_b{=}CH\text{-}CH_2O$), 6.10-6.20 (1H, m, $CH_2{=}CH\text{-}CH_2O$), 7.29 (1H, s, Har), 7.38 (1H, s, Har); δ_C(100 MHz, $CDCl_3$) 56.45, 56.51, 68.49, 101.13, 107.14, 111.69, 116.53, 119.43, 131.81, 138.03, 148.17, 151.88, 156.28, 165.05; *m/z* 271 (M^+, 67%), 256 (M^+-[CH_3], 55), 245 (M^+-[CN], 13), 231 (M^+-[C_3H_5], 31).

6,7-Dimethoxy-4-(3-methylbutoxy)-quinazoline-2-carbonitrile 13i (R = $(CH_3)_2CH\text{-}CH_2\text{-}CH_2$-) Colourless needles, mp 163°C (from 2-propanol) (Found M^+, 301.1429. $C_{16}H_{19}N_3O_3$ requires *M*, 301.1426); ν_{max} (KBr)/cm^{-1} 3021, 2961, 2237 (CN), 1613, 1578, 1515, 1474, 1462, 1429, 1269, 1170 and 993; δ_H (400 MHz , $CDCl_3$) 1.02 (6H, d, *J* 6.3, $(CH_3)_2CHCH_2CH_2O$), 1.78-1.90 (3H, m, $(CH_3)_2CHCH_2CH_2O$), 4.04 (3H, s, OMe), 4.05 (3H, s, OMe), 4.63 (2H, t, *J* 6.7, $(CH_3)_2CHCH_2CH_2O$), 7.3 (1H, s, Har), 7.35 (1H, s, Har); δ_C(100 MHz, $CDCl_3$) 22.6, 25.32, 37.36, 56.4 (OMe), 56.5 (OMe), 66.86, 100.6, 101.15, 107.12, 111.8, 116.6, 138.25, 148.00, 151.7, 156.15, 165.55; *m/z* 301 (M^+, 11%), 244 (M^+-[$(CH_3)_2CHCH_2CH_2$], 2), 231 (M^+-[$(CH_3)_2CH{=}CH_2$], 100), 216 (M^+-[$(CH_3)_2CH{=}CH_2$, CH_3], 13).

***N*-Arylthiocarbamates: general procedures**

Method A : conventional heating. A stirred mixture of arylisothiocyanate **15** (0.3 g, 2.22 mmol) and sodium hydride (NaH, 0.057 g, 2.44 mmol) in the alcohol (2 ml) was heated at reflux in an oil bath until the starting material had been used up (TLC). The hot solution obtained was filtered, the solvent evaporated and the product purified by column chromatography (light petroleum - dichloromethane).

Method B : microwave experiments. The same reaction mixture was placed in a microwave reactor (Synthewave™ S402 or S1000) in an open flask. The solution was irradiated (with a delay of 10-15 seconds to

obtain the reflux) until the starting isothiocyanate had been used up (TLC). The product was purified as described above.

The same procedures where performed without added base; the reaction times are indicated in Table 3.

***n*-Butyl *N*-phenylthiocarbamate 16a** Colourless needles, mp 61°C (from light petroleum) (Found M^+, 209.0874. $C_{11}H_{15}NOS$ requires *M*, 209.0874); ν_{max} (KBr)/cm^{-1} 3221, 3187, 2964, 2929, 1601, 1557, 1413, 1363, 1222, 1033 and 744; δ_H(400 MHz, $CDCl_3$) 0.96 (3H, t, *J* 7.5, $CH_3CH_2CH_2CH_2O$), 1.44 (2H, sextuplet, *J* 7.5, $CH_3CH_2CH_2CH_2O$), 1.77 (2H, m, $CH_3CH_2CH_2CH_2O$), 4.59 (2H, t, *J* 6.0, $CH_3CH_2CH_2CH_2O$), 7.16-7.34 (5H, m, Har), 8.00 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 13.66, 19.14, 30.48, 72.88, 121.51, 125.34, 128.99, 137.07, 188.79; *m/z* 209 (M^+, 32%), 153 (M^+-[CH_2=$CHCH_2CH_3$], 100), 135 (M^+-BuOH, 18), 120 (M^+-[C_4H_9S], 77%), 93 (M^+-[C_5H_8SO], 75), 77 (C_6H_5, 31).

***n*-Propyl *N*-phenylthiocarbamate 16b** Colourless needles, mp 46°C (from light petroleum) (Found M^+, 195.0714. $C_{10}H_{13}NOS$ requires *M*, 195.0718); ν_{max} (KBr)/cm^{-1} 3229, 1941, 1847, 1734, 1596, 1059, 1197, 1006, 903 and 754; δ_H(400 MHz, $CDCl_3$) 1.01 (3H, t, *J* 7.7, $CH_3CH_2CH_2O$), 1.82 (2H, sextuplet, *J* 7.0, $CH_3CH_2CH_2O$), 4.54 (2H, m, $CH_3CH_2CH_2O$), 7.18-7.35 (5H, m, Har), 8.27 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 10.43, 21.85, 74.52, 121.49, 125.34, 128.96, 137.15, 188.77; *m/z* 195 (M^+, 44%), 153 (M^+-[CH_2=$CHCH_3$], 100), 135 (M^+-PrOH, 43), 120 (M^+-[CH_2=$CHCH_3$, SH], 95), 93 (M^+-[C_4H_6OS], 91), 77 (C_6H_5, 66).

***n*-Ethyl *N*-phenylthiocarbamate 16c** Colourless needles, mp 72°C (from light petroleum) (Found M^+, 181.0561. $C_9H_{11}NOS$ requires *M*, 181.0560); ν_{max} (KBr)/cm^{-1} 3221, 2984, 1596, 1540, 1196, 1032, 904 and 747; δ_H(400 MHz, $CDCl_3$) 1.42 (3H, t, *J* 7.0, CH_3CH_2O), 4.64 (2H, q, *J* 7.0, CH_3CH_2O), 7.17-7.36 (5H, m, Har), 8.41 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 14.01, 68.64, 121.44, 125.20, 128.91, 137.15, 188.47; *m/z* 181 (M^+, 100%), 153 (M^+-[C_2H_4], 16), 148 (M^+-[SH], 15), 135 (M^+-EtOH, 27), 120 (M^+-[C_2H_5S], 91), 93 (M^+-[C_3H_4SO], 44), 77 (C_6H_5, 40).

***n*-Butyl *N*-(2-cyanophenyl)thiocarbamate 16d** Colourless oil, (Found M^+, 234.0834. $C_{12}H_{14}N_2OS$ requires *M*, 234.0826); ν_{max} (KBr)/cm^{-1} 3324, 3097, 2958, 2218 (CN), 1590, 1556, 1411, 1195, 1066 and 827; δ_H(400 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.3, $CH_3CH_2CH_2CH_2O$), 1.43 (2H, sextuplet, *J* 7.6, $CH_3CH_2CH_2$-CH_2O), 1.77 (2H, m, $CH_3CH_2CH_2CH_2O$), 4.55 (2H, t, *J* 6.7, $CH_3CH_2CH_2CH_2O$), 7.27 (1H, td, *J* 1.2 and 6.7, Har), 7.60 (1H, dd, *J* 1.2 and 8.2, Har), 7.64 (1H, dd, *J* 1.2 and 7.9, Har), 8.00 (1H, s(b), Har), 8.39 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 13.68, 19.11, 30.27, 72.93, 106.00, 116.06, 124.06, 125.58, 132.83, 133.55, 149.00, 188.76; *m/z* 234 (M^+, 21%), 178 (M^+-[CH_2=$CHCH_2CH_3$], 83), 160 (M^+-BuOH, 65), 145 (M^+-[CH_2=$CHCH_2CH_3$, SH], 43), 118 (M^+-[C_5H_8OS], 100), 102 (C_6H_4CN, 31).

***n*-Butyl *N*-(4-methoxyphenyl)thiocarbamate 16e** Colourless needles, mp < 50°C (from light petroleum) (Found M^+, 239.0979. $C_{12}H_{17}NO_2S$ requires *M*, 239.0979); ν_{max} (KBr)/cm^{-1} 3221, 2958, 1595, 1510, 1463, 1405, 1363, 1246, 1178, 1033 and 828; δ_H(400 MHz, $CDCl_3$) 0.86 (3H, t, *J* 7.3, $CH_3CH_2CH_2CH_2O$), 1.32 (2H, sextuplet, *J* 7.3, $CH_3CH_2CH_2CH_2O$), 1.65 (2H, m, $CH_3CH_2CH_2CH_2O$), 3.70 (3H, s, OMe), 4.90 (2H, t, *J* 6.1, $CH_3CH_2CH_2CH_2O$), 6.80 (2H, d, *J* 8.8, Har), 7.12 (2H, d, *J* 8.3, Har), 8.10 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 13.42, 18.91, 30.27, 55.18, 72.15, 113.87, 123.36, 130.05, 156.90, 188.08; *m/z* 239 (M^+, 100%), 183 (M^+-[CH_2=$CHCH_2CH_3$], 100), 165 (M^+-BuOH, 14), 150 (M^+-[CH_2=$CHCH_2CH_3$, SH], 24), 123 (M^+-[C_5H_8OS], 72), 108 (M^+-[C_5H_9NOS], 78).

***n*-Propyl *N*-(4-methoxyphenyl)thiocarbamate 16f** Colourless needles, mp < 50°C (from light petroleum) (Found M^+, 225.0817. $C_{11}H_{15}NO_2S$ requires *M*, 225.0823); ν_{max} (KBr)/cm^{-1} 3219, 2966, 1510, 1406, 1298, 1249, 1191 and 830; δ_H(400 MHz, $CDCl_3$) 0.97 (3H, t, *J* 7.35, $CH_3CH_2CH_2O$), 1.78 (2H, m, $CH_3CH_2CH_2O$), 3.81 (3H,s, OMe), 4.51 (2H, t, *J* 6.1, $CH_3CH_2CH_2O$), 6.86 (2H, d, *J* 9.0, Har), 7.16 (2H, d, *J* 8.2, Har), 8.26 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 10.43, 21.88, 55.41, 74.27, 114.09, 123.61, 130.09, 157.25, 188.68; *m/z* 225 (M^+, 100%), 183 (M^+-[CH_2=$CHCH_3$], 73), 165 (M^+-PrOH, 12), 150 (M^+-[CH_2=$CHCH_3$, SH], 19), 123 (M^+-[C_4H_6OS], 37), 108 (M^+-[C_5H_9NOS], 76).

***n*-Butyl *N*-(4-cyanophenyl)thiocarbamate 16g** Colourless needles, mp 94°C (from light petroleum) (Found M^+, 234.0834. $C_{12}H_{14}N_2OS$ requires *M*, 234.0826); ν_{max} (KBr)/cm^{-1} 3224, 3042, 2957, 2220 (CN), 1590, 1504, 1400, 1195 and 827; δ_H(400 MHz, $CDCl_3$) 0.98 (3H, t, *J* 7.3, $CH_3CH_2CH_2CH_2O$), 1.46 (2H, m, $CH_3CH_2CH_2CH_2O$), 1.81 (2H, m, $CH_3CH_2CH_2CH_2O$), 4.59 (2H, t, *J* 6.5, $CH_3CH_2CH_2CH_2O$), 7.50 (2H, s(b), Har), 7.63 (2H, d, *J* 8.7, Har) 8.39 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 13.72, 19.19, 30.39, 72.93, 107.92, 118.57, 120.98, 133.27, 141.05, 188.47; m/z 234 (M^+, 21%), 178 (M^+-[CH_2=$CHCH_2CH_3$], 87%), 160 (M^+-BuOH, 60%), 145 (M^+-[CH_2=$CHCH_2CH_3$, SH], 48), 118 (M^+-[C_5H_8OS], 100), 102 (C_6H_4CN, 34).

***n*-Propyl *N*-(4-cyanophenyl)thiocarbamate 16h** Colourless needles, mp 99°C (from light petroleum) (Found M^+, 220.0680. $C_{11}H_{12}N_2OS$ requires *M*, 220.0670); ν_{max} (KBr)/cm^{-1} 3306, 3096, 2977, 2228 (CN), 1606, 1586, 1522, 1389, 1321, 1200, 1058, 1007 and 839; δ_H(400 MHz, $CDCl_3$) 0.99 (3H, t, *J* 7.3, $CH_3CH_2CH_2O$), 1.82 (2H, sextuplet, *J* 7.0, $CH_3CH_2CH_2O$), 4.53 (2H, t, *J* 6.7, $CH_3CH_2CH_2O$), 7.48 (2H, s(b), Har), 7.61 (2H, d, *J* 8.8, Har), 8.73 (1H, s, *NH*-CS); δ_C(100 MHz, $CDCl_3$) 10.43, 21.75, 74.42, 107.91, 118.49, 120.96, 133.21, 141.01, 188.43; *m/z* 220 (M^+, 44%), 178 (M^+-[CH_2=$CHCH_3$], 80), 160 (M^+-PrOH, 77), 145 (M^+-[CH_2=$CHCH_3$, SH], 55), 118 (M^+-[C_4H_6OS], 100), 102 (C_6H_4CN, 46).

***n*-Butyl *N*-(2,5-dimethoxy)thiocarbamate 16i** Colourless oil (Found M^+, 269.1093. $C_{13}H_{19}NO_3S$ requires *M*, 269.1086); ν_{max} (film)/cm^{-1} 3400, 2967, 2837, 1603, 1526, 1223, 1055, 1024 and 790; δ_H(400 MHz, $CDCl_3$) 0.95 (3H, t, J 7.4, $CH_3CH_2CH_2CH_2O$), 1.46 (2H, sextuplet, $CH_3CH_2CH_2CH_2O$), 1.79 (2H, s(b), $CH_3CH_2CH_2CH_2O$), 3.74 (3H, s, OMe), 3.80 (3H, s, OMe), 4.58 (2H, s(b), $CH_3CH_2CH_2CH_2$-O), 6.58 (1H, dd, *J* 2.7 and 8.9, Har), 6.77 (1H, d, *J* 8.9, Har), 7.36 (1H, s(b), Har), 8.73 (1H, s(b), NHCS); δ_C(100 MHz, $CDCl_3$) 13.68, 19.17, 30.51, 55.64, 56.21, 72.93, 107.56, 108.89, 110.99, 127.46, 142.29, 153.42, 188.35; *m/z* 269 (M^+, 54%), 238 (M^+-OMe, 4%), 213 (M^+-[CH_2=$CHCH_2CH_3$], 93), 95 (M^+-BuOH, 23), 182 (M^+-[CH_2=$CHCH_2CH_3$, OMe], 48), 180 (M^+-[CH_2=$CHCH_3$, SH], 21), 165 (M^+-[CH_2=$CHCH_3$, SH, Me], 17), 138 (M^+-[C_5H_9NOS], 100).

***n*-Propyl *N*-(2,5-dimethoxy)thiocarbamate 16j** Colourless oil (Found M^+, 255.0926. $C_{12}H_{17}NO_3S$ requires *M*, 255.0931); ν_{max} (film)/cm^{-1} 3403, 2965, 2834, 1600, 1526, 1485, 1224, 1045, 1024 and 796; δ_H(400 MHz, $CDCl_3$) 1.04 (3H, t, J 7.4, $CH_3CH_2CH_2O$), 1.87 (2H, s(b), $CH_3CH_2CH_2O$), 3.76 (3H, s, OMe), 3.83 (3H, s, OMe), 4.56 (2H, s(b), $CH_3CH_2CH_2O$), 6.60 (1H, dd, *J* 2.7 and 8.9, Har), 6.79 (1H, d, *J* 9.0, Har), 7.37 (1H, s(b), Har), 8.75 (1H, s(b), NHCS); δ_C(100 MHz, $CDCl_3$) 10.48, 21.88, 55.65, 56.21, 74.68, 107.68, 108.70, 110.90, 127.47, 142.34, 153.42, 188.39; *m/z* 255 (M^+, 91%), 224 (M^+-OMe, 9%), 213 (M^+-[CH_2=$CHCH_3$], 80), 95 (M^+-PrOH, 17), 182 (M^+-[CH_2=$CHCH_3$, OMe], 52), 180 (M^+-[CH_2=$CHCH_3$, SH], 24), 165 (M^+-[CH_2=$CHCH_3$, SH, Me], 17), 137 (M^+-[C_4H_7NOS], 100).

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