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Multistep synthesis of thiazoloquinazolines under microwave irradiation in solution

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Abstract

Thiazolo[5,4-*f*]quinazolines are synthesised in six or seven steps from 2-amino-5-nitrobenzonitrile. Both heterocyclic rings are fused onto the central benzene ring via imino-1,2,3-dithiazoles which are readily obtained from primary aromatic amines and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt). Four of the steps were improved in yield or reaction time or both, compared to conventional heating, by microwave irradiation of solutions of the reactants in a focused open microwave oven.

Keywords: medium ring heterocycles; microwave heating; thiazoles; quinazolines.

N-Arylimino-1,2,3-dithiazoles **2** are readily prepared in high yield from anilines and 4,5-dichloro-1,2,3-dithiazole chloride **1**.[1,2] These imines are highly versatile intermediates in heterocyclic synthesis, undergoing a variety of reactions initiated by nucleophilic attack at different sites on the dithiazole ring. For example, they can be converted into 2-cyano derivatives of benzothiazoles **3** or 4-alkoxyquinazolines **4** (Scheme 1).[2,3] In a search for new polyheterocyclic systems of potential pharmacological value, we have now combined these two processes in the synthesis of the rare thiazolo[5,4-*f*]quinazolines, by starting from a benzene derivative and fusing on both heterocyclic rings via iminodithiazoles.

As part of our work on the application of microwave irradiation of reaction solutions,[4] we have transposed several of the present reactions to a focused microwave oven (open oven, monomode system) especially designed for organic synthesis, and have achieved striking reductions in reaction times, better yields and cleaner reactions than for the purely thermal processes. Conventional heating and microwave irradiation of the reactions are compared.

Synthesis of the rare thiazolo[5,4-*f*]quinazoline ring was performed in six steps from commercially available 2-amino-5-nitrobenzonitrile (Scheme 2); preliminary studies showed that it is better to create the quinazoline ring before the thiazole ring.

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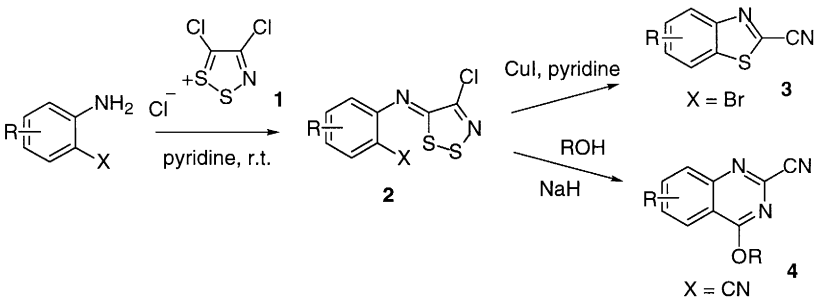
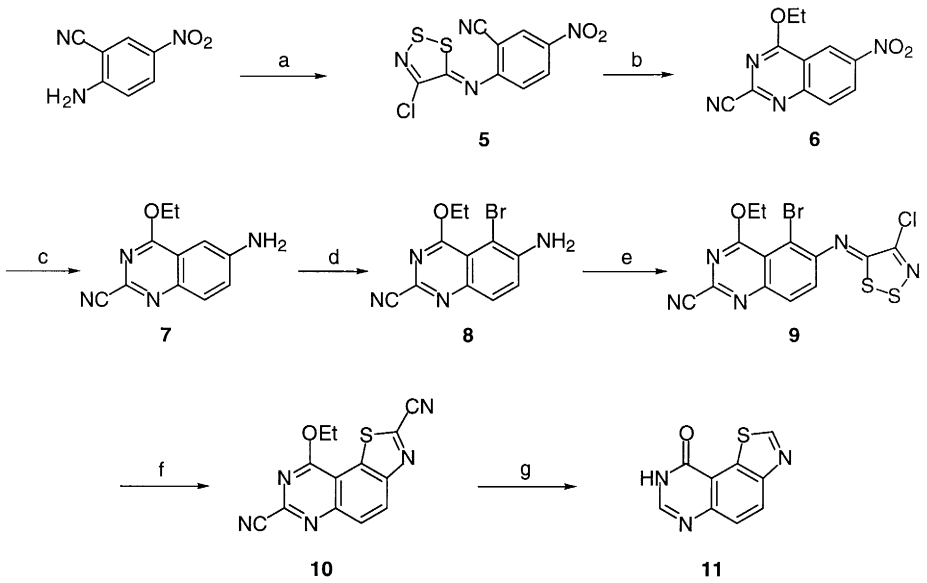


Scheme 1.



Scheme 2. Reagents and conditions (for time and yields of steps b, c, f and g: see Table 1): (a) **1**, pyridine, rt, 10 h, 78%; (b) NaH, EtOH, reflux; (c) $SnCl_2 \cdot 2H_2O$, EtOH, 70°C; (d) Br_2, CH_3COOH, rt, 4 h, 74%; (e) **1**, pyridine, rt, 4 h, 66%; (f) CuCN, pyridine, reflux; (g) HCl, reflux

Using a standard method,[2] the starting amine was condensed with 4,5-dichloro-1,2,3-dithiazolium chloride **1** in dichloromethane, in the presence of pyridine, to give the imino-1,2,3-dithiazole **5**.[5] Heating of this imine with sodium hydride in ethanol at reflux led to the desired 4-ethoxy-6-nitroquinazoline-2-carbonitrile **6**. Reduction of the nitro compound to the corresponding amino compound, **7**, followed by *ortho*-bromination of the aminoquinazoline was easily performed in good yield. The dithiazole **9**, obtained by condensation of amine **8** with the salt **1**, was converted exclusively into the angular 2,7-dicyano-9-ethoxythiazoloquinazoline **10**[6] with cuprous iodide.[7] Complete decyanation of compound **10** by hydrolysis and decarboxylation gave the thiazolo[5,4-*f*]quinazolinone **11**.[6,8] The thiazoloquinazolines show interesting cytotoxic activity against L1210 tumor cells which is being investigated.[9]

The recent development and use of open focused microwave ovens[10] allow comparison of conventional heating (oil or metal bath) and microwave irradiation. The experimental conditions used in our work were similar, with the same concentration of starting material and volume of solvent.[11]

The data collected in Table 1 confirm that focused microwave irradiation in an open oven is a powerful technique for accelerating thermal organic reactions. Transposition of four steps of the synthesis of thiazoloquinazolines to microwave irradiation of solutions gave the desired compounds in yields

comparable, and sometimes better, to those obtained by conventional heating. The overall time for the synthesis was considerably reduced, the reactions were cleaner and the products were easily purified.

Table 1
Conventional heating versus microwave irradiation for steps b,c,f and g of Scheme 2[a]

Step	Starting material	Product	Conventional heating[b] reaction time (min)	Yield (%)	Microwave irradiation[c] reaction time (min)	Yield (%)
b	**5**	**6**	640	37	80	61
c	**6**	**7**	60	72	10	94
f	**9**	**10**	90	50	20	53
g	**10**	**11**	60	49	10	50

a) All the reactions were performed 3 times and the reaction time and yields given are the average values; b) oil bath; c) microwaves, 300W.

In conclusion, we have described a rapid multistep synthesis of the rare[8] thiazolo[5,4-*f*]quinazoline ring via Appel salt chemistry, and provided further examples of the utility of microwaves in organic synthesis in the presence of solvents. New open focused microwave reactors minimize the risks of explosions and hazardous bumping previously experienced with multimode systems (domestic ovens) and make it possible to develop rapid multistep syntheses in which a high proportion of the reactions is performed under microwave irradiation. The extension of such experiments to a larger scale is now being investigated.

Acknowledgements

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5. Spectral data for compounds **5**–**9** are consistent with the assigned structures.
6. Selected data for compounds **10** and **11**. 9-Ethoxythiazolo[5,4-*f*]quinazoline-2,7-dicarbonitrile **10**: brown powder, mp 208–210°C (from isopropanol) (Found: M^+, 281.0369. $C_{13}H_7N_5OS$ requires: M, 281.0371); ν_{max} (KBr)/cm^{-1} 3074, 2922, 2242 (CN), 1567, 1532, 1503, 1386, 1386, 1338, 1145, 1026, 999, and 852; δ_H(400 MHz, $CDCl_3$) 1.69 (3H, t, *J* 7.1 Hz,

C*H*$_3$-CH$_2$O), 4.90 (2H, q, *J* 7.1 Hz, CH$_3$-C*H*$_2$-O), 8.23 (1H, d, *J* 9.15 Hz, Har), 8.68 (1H, d, *J* 9.15 Hz, Har); δ_C(100 MHz, $CDCl_3$), 14.4, 66.5, 111.9, 112.4, 115.8, 128.7, 129.5, 131.3, 140.3, 140.8, 151.6, 152.4, 165.6; *m/z* 281 (M^+, 28%), 266 (12), 253 (100), 237 (14), 226 (10). Thiazolo[5,4-*f*]quinazolin-9(8*H*)one **11**: white needles, mp>260°C (from isopropanol) (found: M^+, 203.0159. $C_9H_5N_3OS$ requires: *M*, 203.0153); ν_{max} (KBr)/cm^{-1} 3073, 1684, 1587, 1400, 1380, 1346, 1296, 1239, 1172, 987 and 830; δ_H(400 MHz, $CDCl_3$+ D_2O) 7.84 (1H, d, *J* 8.7 Hz, Har), 8.29 (1H, s, N=CH-S), 8.49 (1H, d, *J* 8.7 Hz, Har), 9.55 (1H, s, N=CH-N); δ_C(100 MHz, $CDCl_3$) 116.9, 125.9, 128.9, 129.6, 145.4, 147.6, 151.8, 159.0, 159.8; *m/z* 203 (M^+, 100%), 176 (23), 148 (27), 121 (18).

7. Besson, T.; Dozias, M.-J.; Guillard, J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3925–3926.
8. For the only other report of this ring system, see: Kanazawa, H.; Senga, K.; Tamura, Z. *Chem. Pharm. Bull.* **1985**, *33*, 618–625.
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10. (a) Commarmot, R.; Didenot, R.; Gardais, J. F. French patent 2 560 529 (1985), Rhône-Poulenc/Prolabo, *Chem. Abst.* **1986**, *105*, 17442; (b) Jacquault, P. (Prolabo company) European Patent. 545995 AI (21-12-92), 1992.
11. Focused microwave irradiations were carried out at atmospheric pressure with a Synthewave S402 (capacity of the quartz reactors used: 10 and 70 ml) Prolabo microwave reactor (300 W, monomode system) which has a quartz reactor, visual control, irradiation (300 W) monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC). Equipment of the oven was completed by an external stirring system, a condenser and dropping funnel allowing conditions close to those involved in classical methods; it is also possible to work under dry atmosphere or in vacuo if necessary. The ratio between the quantity of reactant and the solvent is very important; if it is too large, hazardous solvent bumping in the reactor may result. The best conditions involve a concentration of 3–5% of the starting material.