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Microwave assisted solvent-free synthesis of pyrazolo[3,4-*b*]quinolines and pyrazolo[3,4-*c*]pyrazoles using *p*-TsOH

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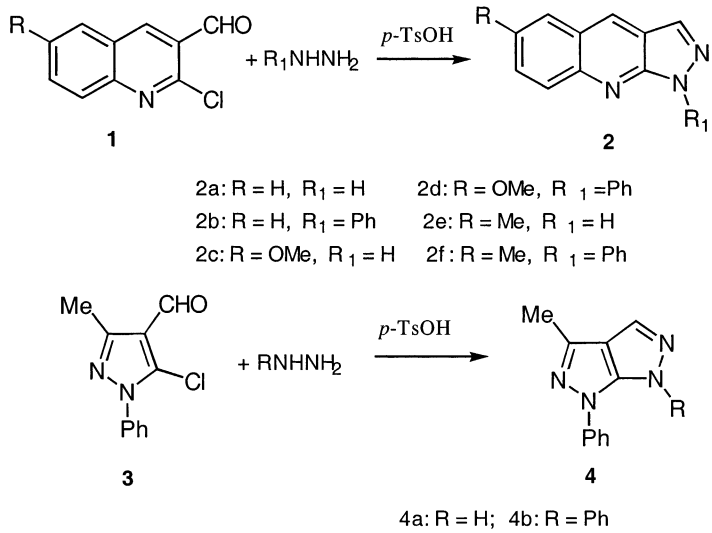
Abstract—Pyrazolo[3,4-*b*]quinolines and pyrazolo[3,4-*c*]pyrazoles have been synthesized from β-chlorovinylaldehydes and hydrazine hydrate/phenylhydrazine using *p*-TsOH under microwave irradiation.

Pyrazole derivatives exhibit pharmacological activities such as hypotensive, antibacterial, anti-inflammatory and antitumor properties. In particular, condensed pyrazoles are known for various biological activities, e.g. pyrazolo[3,4-*b*]quinolines as potential antiviral,[1] antimalarial,[2] lowering of serum cholesterol;[3] pyrazolo[3,4-*c*]pyrazoles are useful for the treatment of esophageal and gastrointestinal mucosa injury,[4] brain injury,[5] and also as immunostimulatory,[6] antianginal[7] and antitumor[8] agents. Similarly β-chlorovinylaldehydes are important synthons used for the synthesis of a variety of heterocyclic systems like pyran-2-ones,[9] pyrrole derivatives,[10] pyrazolo[3,4-*b*]pyridines,[11] pyrazolo[4,3-*c*] benzothiazines,[12] etc.

A number of methods are available for the synthesis of condensed pyrazoles, the most efficient and commonly used method involves the reaction of β-chlorovinylaldehydes with hydrazine hydrate or phenylhydrazine. In 1986, a two-step synthesis of pyrazolo[3,4-*b*]quinolines



Scheme 1.

Keywords: aldehydes; solvent-free conditions; *p*-toluenesulfonic acid; microwave activation; cyclizations.
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was reported.[13] In this synthesis, the hydrazones and oximes of 2-chloro-3-formylquinolines prepared in a first step resist the attack of hydrazine on the carbon bearing chlorine atom even under drastic conditions, since they exist in E-form. Thus, the adopted strategy involved the previous protection of a CHO group followed by attack of hydrazine on the carbon bearing a chlorine atom, the deprotection of CHO group and the subsequent cyclization to give pyrazolo[3,4-*b*]-quinolines. Recently, a one-pot synthesis from 2-chloro-3-formylquinolines and hydrazine hydrate/phenylhydrazine hydrochloride in refluxing ethanol has been reported,[14] which involved a reaction time of 5/7 h and gives a 44–82% yield. Similarly, the synthesis of pyrazolo[3,4-*c*]pyrazoles[15] is a two-step process involving formation of hydrazones followed by cyclization by fusion at 150–160°C with a 90–93% yield, while a one-step synthesis took 12–14 hours, giving a 65–70% yield in refluxing methanol.

The upcoming area of 'green chemistry', carrying out organic reactions under solvent-free dry media conditions[16] aims at reducing the use of toxic solvents, thus preventing pollution in organic synthesis 'at source', while reactions under microwave irradiation[17] are clean, fast and economical.

Keeping in mind the biological importance of condensed pyrazoles, our interest[18] in devising solvent-free procedures and their association with microwave activation,[19] we describe here the synthesis[20] of pyrazolo[3,4-*b*]quinolines and pyrazolo[3,4-*c*]pyrazoles using *p*-TsOH as catalyst (Scheme 1). Starting materials 2-chloro-3-formylquinolines[21] and 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde[22] were prepared by literature methods.

Different solid supports, including silica gel, various aluminas, strongly acidic montmorillonite (K10), $HCOOH/SiO_2$ and *p*-TsOH were checked to define the most effective (Table 1).

The reaction has also been carried out without adding any support (neat conditions), which could be expected to be the most economical method. But unfortunately lower yields were obtained (5 min: 38%; 15 min: 42%; 30 min: 51%), which may be due to the low temperature (respectively, 65–67 and 68–70°C after 15 and 30 min). From these results, it is obvious that *p*-TsOH is the most adaptable and simplest catalyst for the synthesis of **2a**, as work-up is simply reduced to treatment with ice-cold water. We have thus extended these conditions to the synthesis of pyrazolo[3,4-*b*]quinolines (**2a**–**f**) and pyrazolo[3,4-*c*]pyrazoles (**4a**–**b**) with very satisfactory results (78–97%) (Table 2).

Finally, in order to check the possible intervention of specific (non-thermal) microwave effects, the reaction (in the case of compound **2a**) has been carried out using a pre-heated oil-bath for the same duration and at the same final temperature (127–130°C) as measured at the end of exposure during the microwave experiment. It has been found that reaction proceeds with 30% yield under thermal conditions in 1.5 minutes. The remaining product was found to be the hydrazone. However, if heating is continued for 22 minutes in the oil-bath, the

Table 1. Effect of solid support in dry media for the synthesis of **2a** under microwave irradiation (power = 300 W)

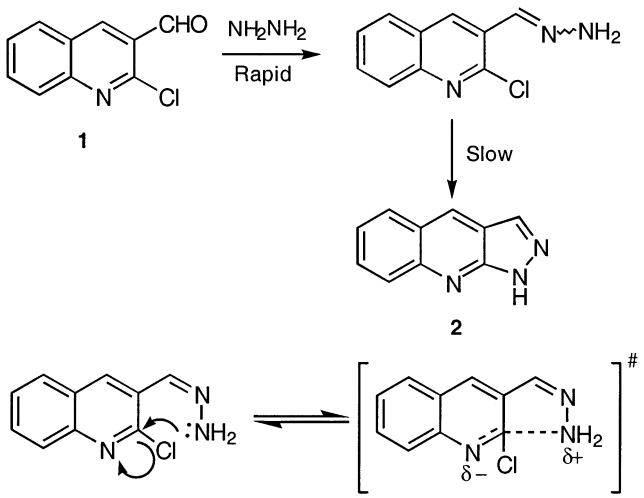
Support	Time (min)	Yield (%)	Temperature[a] (°C)
No	5	38	75–77
EG + AcOH[b]	5	75	130–132
Alumina	10	43	99–101
Silica gel	10	40	104–106
K10	10	25	106–108
$HCOOH/SiO_2$	15	10	93–95
***p*-TsOH**	**1.5**	**97 (30)[c]**	**127–130**

[a] Final temperature was measured by immersing a glass thermometer in the reaction mixture at the end of exposure during a microwave experiment.
[b] Ethylene glycol containing a small amount (two drops) of acetic acid.
[c] Results obtained under classical heating using a thermostated oil bath at 130°C within 1.5 minutes.

Table 2. Microwave synthesis of pyrazolo[3,4-*b*]quinolines (**2a**–**f**) and pyrazolo[3,4-*c*]pyrazoles (**4a**–**b**) (1 mmol) using *p*-TsOH (100 mg) as the catalyst (power = 300 W)

Product	Irradiation time (min)	Yield[a] (%)	Mp (°C) found/reported
2a	1.5	97	205–207/203–204[14]
2b	1.5	78	170 (d)/172 (d)[14]
2c	1.5	92	218–220/217–218[14]
2d	2	85	149 (d)/150 (d)[14]
2e	1.5	92	177 (d)/175 (d)[14]
2f	2	90	180–181/176–178[14]
4a	2	96	202–203/200[15]
4b	2.5	94	173–174/170–171[15]

[a] Yields of isolated products.



Scheme 2.

remaining hydrazone also cyclized to give **2a** with a comparable yield (88%) (Scheme 2).

The noticeable rate enhancement due to a specific MW effect is consistent with the reaction mechanism (S_NAr) if we admit that the kinetic rate determining step is the nucleophilic attack of amino group on the chloro quinoline ring. As the transition state is more polar than the ground state due to development of a dipole, a greater stabilization results with MW as dipole–dipole interactions are increased and favored.

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19. Reactions were carried out in a BPL 800 T microwave oven having a maximum power output of 800 watts.
20. *General procedure for the synthesis of condensed pyrazoles **2a–f** and **4a–b***. Appropriate β-chlorovinylaldehydes **1** or **3** (1 mmol) and hydrazine hydrate (4 mmol) or phenylhydrazine (1.25 mmol) were introduced in a beaker (50 mL). A small amount of *p*-TsOH (100 mg) was added and properly mixed with the help of a glass rod. The so-obtained paste was irradiated in a microwave oven at a power output of 300 W for the appropriate time (Table 2). After irradiation, cold water (25 mL) was added. The obtained solid was collected, washed with water, dried and recrystallized from adequate solvent to afford the desired products in good yield (78–97%).
The structure of the products was confirmed by IR, ^{1}H NMR, mass spectroscopy and comparison with authentic samples prepared according to literature methods.[14,15]
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