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Synthesis of novel 5a,10,14b,15-tetraaza-benzo[*a*]indeno[1,2-*c*]-anthracen-5-one and benzimidazo[1,2-*c*]quinazoline derivatives under microwave irradiation

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Abstract

Novel 5a,10,14b,15-tetraaza-benzo[*a*]indeno[1,2-*c*]anthracen-5-one and benzimidazo[1,2-*c*]quinazoline derivatives were synthesised in good yields in two or three steps from 2-(2-aminophenyl)indole and 2-(2-aminophenyl)benzimidazole. Microwave irradiation in homogeneous phase or in dry media was used in order to improve reactions where conventional heating (metal or oil bath) was limited.

Keywords: large ring heterocycles; microwave activation.

In a search for new polyheterocyclic systems with potential pharmacological values,[1] we planned to prepare new hexacyclic compounds, from 2-(2-aminophenyl)benzimidazole and by fusing the benzimidazo[1,2-*c*]quinazoline and the quinazolin-4-one rings. Exploring the chemistry of 6-mercaptobenzimidazo[1,2-*c*]quinazoline **1** we also prepared two original benzimidazo[1,2-*c*]quinazoline dimers which are related to synthetic dimers recently described as a new class of potent antitumour compounds.[2] Many of the reactions developed in this synthesis were transposed in a focused microwave oven (open oven, monomode system) designed for organic synthesis.[3] Fusion of the quinazolin-4-one ring onto the benzimidazo-[1,2-*c*]quinazoline skeleton was performed via a modified Niementowski reaction[4] and was especially studied under a microwave field. Then,

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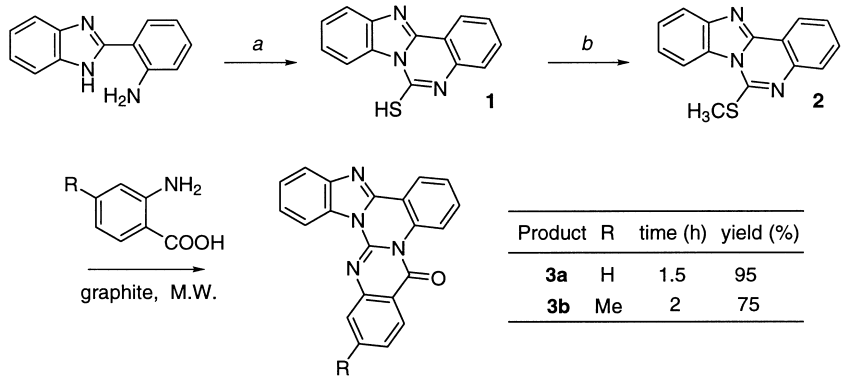
we achieved striking reduction in reaction times, good yields and cleaner reactions than for the purely thermal procedures.

Preparation of 6-mercaptobenzimidazo[1,2-*c*]quinazoline **1**[5] was easily accomplished (95%) at 60°C under microwave irradiation in 55 min by reaction of the starting 2-(2-aminophenyl)benzimidazole with carbon disulphide in the presence of potassium hydroxide (this reaction was also performed in 24 h in an oil bath in a similar yield) (Scheme 1). Our first intention was to fuse the benzimidazo[1,2-*c*]quinazoline and the quinazolin-4-one rings by condensation of the benzimidazo[1,2-*c*]quinazoline **1** and anthranilic acid. Unfortunately, whatever conditions were used (classical thermal heating or microwave irradiation) no product was detected. Transformation of the mercapto group of compound **1** in a better leaving group was expected to favour the first nucleophilic attack of the amino group of anthranilic acid on carbon 6. Then, thermal cyclisation will occur with loss of water, to lead to a new polyheterocyclic skeleton.



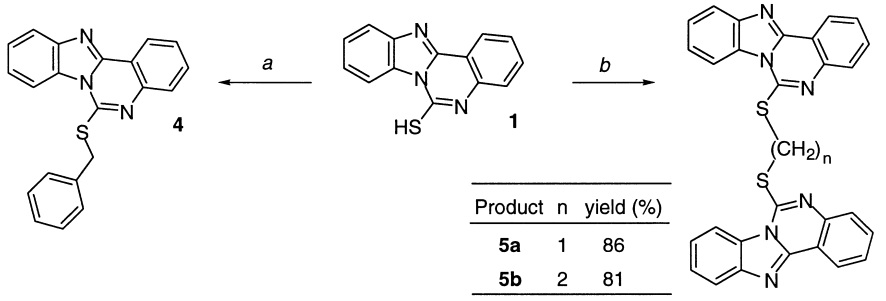
Product	R	time (h)	yield (%)
3a	H	1.5	95
3b	Me	2	75

Scheme 1. Reagents and conditions: (a) CS_2, MeOH/KOH, reflux, MW, 55 min, 95%; (b) CH_3I, NaH/DMF, rt, 5 min, 95%

Treatment of the 6-mercaptobenzimidazo[1,2-*c*]quinazoline **1** with an excess of methyl iodide, in dimethylformamide, in the presence of sodium hydride (1 equiv.) as a base, gave the intermediate 6-methylmercaptobenzimido[1,2-*c*]quinazoline **2**.[5] This method led to a better yield (95%) than the already described procedure (80%).[2] Thermal heating of the two starting compounds (benzimidazoquinazoline **2** and anthranilic acid), neat at 120°C or in butanol at reflux for 48 h, cannot give more than 50% of the attempted product. Transposition of such a process in a microwave oven allowed a reduction of the reaction time (6 h) with no improvement of the yield. In each case a longer heating period gave a complex mixture with degradation products. Inspired by recent work on retro-Diels–Alder reactions with carbon graphite as support,[6] we discovered that irradiation[7] of a mixture of the intermediate **2** and an excess of anthranilic acid (6 equiv.), absorbed on graphite, led to the cyclised 5a,10,14b,15-tetraaza-benzo[*a*]indeno[1,2-*c*]anthracen-5-one **3a**[5,8] in good yield and in a shorter time than for the purely thermal procedures (in similar experimental conditions, with the same quantity of starting materials and graphite, a conventional heating gave a very poor yield for **3a** after 24 h). This process was extended to the 5-methylanthranilic acid to give product **3b**[5,8] in a yield of 75%. Here again, no by-products were detected, reaction was very clean and purification of the product was facilitated.

In view of the above results, we observed that reaction between the mercapto derivative **1** and iodomethane was convenient (95% yield in 5 min), we decided to extend this process to various

halogenated reactants such as benzylbromide, dibromomethane and 1,2-dibromoethane. If the synthesis of the benzylmercaptobenzimido[1,2-*c*]quinazoline **4**, in the conditions described for **2**, was rapid (5 min) and easy (yield: 95%), treatment of **1** with dibromo-derivatives was more difficult (Scheme 2). The reaction was never complete whatever conditions were used (various reaction times, temperatures and heatings). Another method involving potassium carbonate and tetrabutylammonium bromide[9] (TBAB, a phase transfer catalyst) was successful but needed a long heating time (12 h) to provide the dimers **5** in good yields (90% for **5a** and 85% for **5b**). Here again transposition of this procedure at 60°C in a microwave oven allowed a striking reduction in the reaction times (12 h→15 min) in similar yields (86 and 81%).



Product	n	yield (%)
5a	1	86
5b	2	81

Scheme 2. Reagents and conditions: (a) $PhCH_2Br$, NaH/DMF, rt, 5 min, 95%; (b) $Br(CH_2)_nBr$, K_2CO_3/TBAB/DMF, 60°C, MW, 15 min

In conclusion, we have described in this paper the preparation of novel tetraaza-benzo[*a*]-indeno[1,2-*c*]anthracen-5-one derivatives by fusion of the benzimidazo[1,2-*c*]quinazoline and quinazolin-4-one rings. In parallel, we also performed the synthesis of original benzimidazo[1,2-*c*]-quinazoline dimers bridged with polyalkylmercapto linkers. This work is a further example of the utility of microwaves in organic synthesis. When conventional thermal procedures have failed and whatever conditions are needed (in homogeneous phase, e.g. step 1, or in dry media, e.g. step 3) microwaves irradiation can substitute for classical methods allowing development of easy and rapid access to original heterocycles with potent pharmaceutical value.[10]

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7. Focused microwave irradiations were carried out at atmospheric pressure with a Synthewave S402 Prolabo microwave reactor (300 W, monomode system) which has quartz reactors, visual control, irradiation monitored by PC computer, infrared measurement and continuous feedback temperature control (by PC). Equipment of the oven can be 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 a dry atmosphere or in vacuo if necessary.
8. *Typical procedure for the synthesis of compounds* ***3***: A mixture of compound **2** (0.2 g, 0.75 mmol), anthranilic acid (0.374 g, 4.3 mmol) and graphite (2 g) was placed in the microwave oven in a 70 ml quartz vial. The irradiation was programmed at 105 W for 90 min. (after a period of 2–3 min the temperature reached a plateau, 170°C, and remained constant). After cooling, the graphite powder was filtered and washed with dichloromethane. The organic solution was washed with a saturated solution of sodium bicarbonate, and the crude product recrystallized in ethanol. Remarks: (a) in this process 6 equiv. of anthranilic acid are necessary, other experiments with 1, 2 and 4 equiv. of this acid were not satisfactory); (b) the ratio between the quantity of reactant and the graphite is very important; if it is too large or too small, degraded or incomplete reactions were observed.
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