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Convenient and rapid microwave-assisted synthesis of pyrido-fused ring systems applying the *tert*-amino effect

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The microwave-assisted synthesis of pyrido-fused heterocycles was accomplished in an efficient, economically and environmentally friendly route by the application of the *tert*-amino effect as the key ring closure methodology.

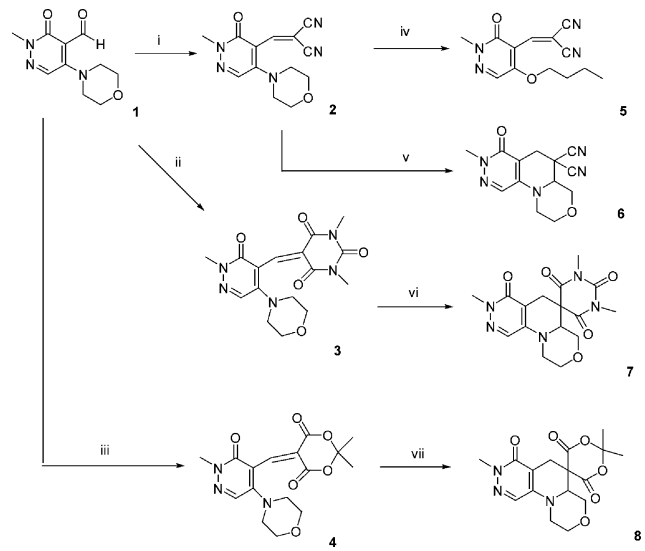
Introduction

Pyrido-fused ring systems are of great importance due to their valuable biological activities. One of the most efficient synthetic pathways to obtain angularly annelated derivatives of such systems involves a three step sequence starting from the easily available *ortho*-functionalized (hetero)aromatic aldehydes. The first step is a nucleophilic substitution to introduce a *tert*-amino group; in the second step the elaboration of a vinylic moiety, generally *via* a Knoevenagel condensation reaction, occurs; finally in the third step, the ring closure between the carbon atoms of the vinyl moiety and the *tert*-amino group is achieved applying the *tert*-amino effect.[1–4] This approach has apparently a serious limitation: the cyclization reaction is a rather slow process, and it often requires prolonged heating in organic solvents with high boiling points to achieve satisfactory conversion.[2,4] As it is known[5] that such processes could highly benefit from microwave irradiation, we were particularly interested in comparing the microwave irradiation protocol with the conventional heating conditions. In this paper we describe our attempts to develop a novel, convenient, rapid and eco-friendly procedure for the preparation of angularly annelated quinolines and pyridopyridazines, based on the microwave-assisted application of the *tert*-amino effect.

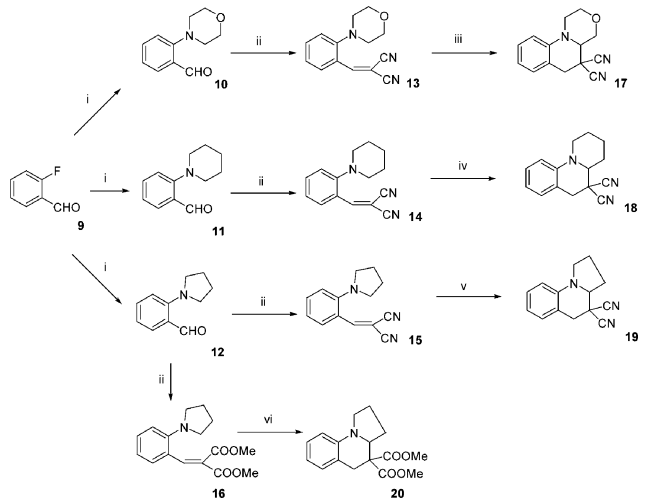
Results and discussion

Two series of (hetero)aromatic aldehydes with an *ortho*-*tert*-amino substituent were prepared in order to investigate the microwave methodology in compounds with significantly different cyclization tendency. These reactions have been studied previously under conventional heating conditions.[1–2] The 5-*tert*-amino-4-vinylpyridazinones **2–4** (Scheme 1), and their benzene analogues **13–16** (Scheme 2) were smoothly synthesized by Knoevenagel condensation of the aldehydes with the corresponding active methylene compounds, according to the procedures described before.[1–4]

In the next step, the cyclization was carried out by operation of the *tert*-amino effect. Under conventional conditions the pyridazino ring system can be obtained after heating at a high temperature for several hours or even days. We now found that the cyclization could be realized in a substantially shorter time upon microwave irradiation applying a dedicated monomode CEM-Discover microwave reactor. Thus, the dimethylbarbituric acid and Meldrum's acid derivatives **3** and **4** underwent ring closure in 5 and 30 min upon microwave irradiation at 230 °C and 200 °C to afford the expected spirocyclic ring systems **7** and **8** in 63% and 73% yields, respectively (Scheme 1, Table 1). Instead of xylene and DMF, *n*-butanol or dimethoxyethane (DME) could be used, making the isolation of the compounds easier. In accordance with our previous observations,[2] we found that the conversion of the acyclic malononitrile derivative **2** to the angularly annelated dinitrile **6** required a prolonged irradiation time (42 min) at 210 °C in DMSO; nevertheless the reaction was far faster compared to conventional heating conditions (44 h). It should be noted that the solvent plays a decisive role in the latter reaction: upon irradiation of compound



Scheme 1 (i) ref. 1; (ii) ref. 2; (iii) ref. 2; (iv) n-BuOH, MW, 240 °C, 40 min, 25%; (v) DMSO, MW, 210 °C, 42 min, 29%; (vi) n-BuOH, MW, 230 °C, 5 min, 63%; (vii) DME, MW, 200 °C, 30 min, 73%.



Scheme 2 (i) ref. 3; (ii) ref. 4; (iii) n-BuOH, MW, 220 °C, 30 min, 96%; (iv) n-BuOH, MW, 200 °C, 3 min, 80%; (v) n-BuOH, MW, 200 °C, 3 min, 84%; (vi) n-BuOH, MW, 220 °C, 15 min, 73%.

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Table 1 Comparison of the cyclization conditions applying the *tert*-amino effect under conventional heating and microwave irradiation conditions

	Conventional heating			Microwave irradiation		
Product	Temp (°C)/ time (h)	Yield (%)	Solvent	Temp (°C)/ time (min)	Yield (%)	Solvent
6	150/44	35	DMSO	210/42	29	DMSO
7	138/2	45	xylene[a]	230/5	63	*n*-BuOH
8	100/5	79	DMF	200/30	73	DME
17	117/35	84	*n*-BuOH	220/30	96	*n*-BuOH
18	117/2	78	*n*-BuOH	200/3	80	*n*-BuOH
19	117/2	82	*n*-BuOH	200/3	84	*n*-BuOH
20	117/22	67	*n*-BuOH	220/15	73	*n*-BuOH

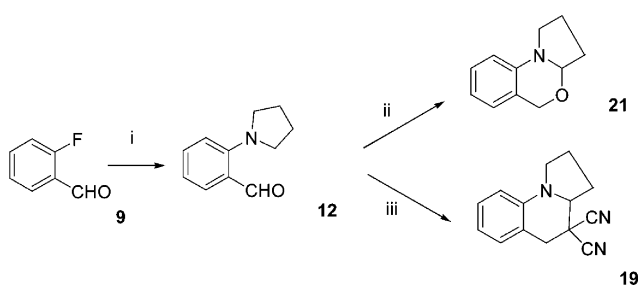
[a] With a catalytic amount of aluminium trichloride.

2 in *n*-butanol, the nucleophilic substitution of the morpholino group proceeded faster than the desired cyclization, and at 70% conversion of the starting compound **2**, the 5-butyloxy derivative **5** has been isolated in 25% yield.

The reaction rates of the cyclizations of the *ortho*-vinyl-*tert*-anilines were also significantly enhanced upon microwave irradiation. Moreover, in all cases the ring closure could be performed in *n*-butanol without the problem of simultanous nucleophilic exchange of the *tert*-amino group by *n*-butyloxy. Thus, the microwave irradiation of solutions of the piperidino and pyrrolidino derivatives **14** and **15** at 200 °C for 3 min afforded the fused products **18** and **19** in high yields (Scheme 2, Table 1). The cyclization of the morpholino analogue **13** required a slightly higher temperature of 220 °C for 30 min, compared to 35 h under conventional heating conditions, and the pyrido-fused ring system **17** was isolated in almost quantitative yield.

Replacement of the cyano groups by the less electron-withdrawing ester groups decreased the reaction rate as expected.[1,2] Accordingly, cyclization of **16** needed a higher temperature (220 °C) and a longer reaction time (15 min) compared to that of the malononitrile derivative **15** (200 °C, 3 min).

As the next step towards real green chemistry, we investigated the replacement of the organic solvent by water. This, in combination with microwave irradiation,[6] should render the procedure highly cost-effective and environmentally friendly. A survey of the literature revealed that both condensation and cyclization reactions, such as aldol-like condensations, Diels–Alder cyclizations, even a domino Knoevenagel–Diels–Alder process, could be performed in water as the sole solvent.[7] As a proof of concept, we investigated the conversion of the *ortho*-fluorobenzaldehyde **9** into the tricyclic **19**. The first intermediate, the *ortho*-pyrrolidinobenzaldehyde (**12**) could be obtained by substitution of the fluorine with pyrrolidine upon controlled microwave irradiation of an aqueous suspension of **9** in the presence of potassium carbonate (Scheme 3). Interestingly, it was found that



Scheme 3 (i) Pyrrolidine, K_2CO_3, H_2O, MW, 130 °C, 3 min; (ii) K_2CO_3, H_2O, MW, 210 °C, 50 min, 28%; (iii) $CH_2(CN)_2$, H_2O, MW, 100 °C, 10 min, then 1 drop of TFA, 200 °C, 3 min, 50%.

further irradiation of **12** at a higher temperature (210 °C) for 50 min afforded the pyrrolobenzoxazine **21** in 28% yield.[8] To obtain the desired tricyclic compound **19**, a powerful one-pot procedure was elaborated. After microwave irradiation of the mixture of the aldehyde **12** and malonitrile at 100 °C for 10 min, one drop of trifluoroacetic acid (TFA) was added to the reaction mixture and irradiation was continued at 200 °C for 3 min. The desired compound **19** could be isolated in 50% yield, starting from **12**.

Conclusions

The development of a new, cost-efficient, microwave-assisted procedure for the synthesis of pyrido-fused ring systems, applying the *tert*-amino effect, has been described. Typically, reactions that required hours or even days under conventional heating conditions, could be completed within 3–42 min under microwave irradiation conditions, with minimum energy demands. The isolated yields obtained with the microwave-assisted procedures, have been found to be at least comparable or even superior to those obtained under conventional heating conditions. Moreover, in a case study for the preparation of a tricyclic angularly annelated compound, an operationally very simple, environmentally friendly protocol was also elaborated, starting from a commercially available aldehyde, using water as the sole solvent in all reaction steps, and integrating the Knoevenagel condensation and the subsequent cyclization into a one-pot reaction.

Based on these results, the new protocols we have developed can be regarded as practical and viable green procedures.

Experimental

General

Melting points were determined using a Reichert–Jung Thermovar apparatus or an Electrothermal 9200 digital melting point apparatus, and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WM 250, Bruker Avance 300 or on a Bruker AMX 400 instrument, using $CDCl_3$ as solvent unless otherwise stated. The ^{1}H and ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane, or using the residual solvent signal as an internal reference. Mass spectra were recorded by using a Kratos MS50TC and a Kratos Mach III data system. The ion source temperature was 150–250 °C as required. For thin layer chromatography, analytical TLC plates (Alugram SIL G/UV_{254} and 70–230 mesh silicagel (E.M.Merck)) were used. Pyridazinecarbaldehyde **1** was prepared according to the published procedure,[2] whereas *ortho*-fluorobenzaldehyde **9** was purchased from Aldrich. Compounds **2–4**, **6–8**, **10–20**, **21** have melting points and spectral data identical to the published values.[1–4,8]

Microwave irradiation experiments

A monomode CEM-Discover microwave reactor (CEM Corporation P.O. Box 200 Matthews, NC 28106) was used in the standard configuration as delivered, including proprietary software. All experiments were carried out in sealed large (10 mL) microwave process vials.

Nucleophilic substitution reaction of 2

2-(5-Butyloxy-2-methyl-3-oxo-2*H*-pyridazin-4-ylmethylene)-malonitrile (5). A solution of **2** (0.2 mmol) in *n*-butanol (3 mL) was irradiated at 240 °C for 40 min at 300 W maximum power. The reaction mixture was cooled to ambient temperature and the solvent was evaporated *in vacuo*. The residue was subjected to flash chromatography on silica (eluent: dichloromethane–hexane 9 : 1) to give starting material **2** (30%) and **5** (25%). White needles, mp 151–153 °C (methanol). ^{1}H NMR ($CDCl_3$): δ 8.84 (s, 1H), 8.19 (s, 1H), 4.59 (t, 2H, J = 7.6 Hz), 3.86 (s, 3H), 1.88 (m, 2H), 1.55 (m, 2H), 1.02 (t, 3H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$): δ 165.7, 158.4, 147.6, 143.5, 137.7, 118.6, 114.2, 102.0, 69.3, 40.1, 30.9, 19.5, 14.2. DEPT ($CDCl_3$): 143.5, 137.7, −69.3, 40.1, −30.9, −19.5, 14.1. MS (CI): m/z (%) = 259 (100) [MH^+]. HR-MS (EI): $C_{13}H_{14}N_4O_2$ Calcd. 258.11168, found 258.11177.

Ring closure reactions of vinylpyridazinones 2–4

2-Methyl-1-oxo-2,5,6,8,8a,10-hexahydro-1*H*-7-oxa-2,3,4b-triaza-phenanthrene-9,9-dicarbonitrile (6). A solution of **2** (0.2 mmol) in DMSO (3 mL) was irradiated at 210 °C for 42 min at 200 W maximum power. The reaction mixture was cooled to ambient temperature, extracted with ether (3 × 10 mL) and washed with brine. The combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo* and the residue was triturated with petroleum ether (bp 60–80 °C) to give **6** in 29% yield.

1′,3,3′-Trimethylspiro-(3,4,5,6,6a,7,9,10-octahydropyridazino[5′,4′:5,6]pyrido-[2,1-c][1,4]oxazine-6,5′-(hexahydropyrimidine)]-2′,4,4′,6′-tetraone (7). A solution of **3** (0.2 mmol) in *n*-butanol (3 mL) was irradiated at 230 °C for 5 min at 300 W maximum power. The reaction mixture was cooled to ambient temperature, the solvent was evaporated *in vacuo* and the residue was triturated with petroleum ether to give **7** in 63% yield.

2,2,3′-Trimethylspiro[dihydro-4*H*-[1,3]dioxane-5,6′-(3′,4′,5′,6′,6a′,7′,9′,10′-octahydropyridazino[5′,4′:5,6]pyrido[2,1-c][1,4]oxazine)]-4,4′,6-trione (8). A solution of **4** (0.2 mmol) in DME (3 mL) was irradiated at 200 °C for 30 min at 300 W maximum power. The reaction mixture was cooled to ambient temperature, the solvent was evaporated *in vacuo* and the residue was crystallized from ethanol to give **8** in 73% yield.

General procedure for the preparation of 17–20

A solution of a compound **13–16** (0.2 mmol) in *n*-butanol (3 mL) was irradiated under conditions described in Table 1 at 300 W maximum power. The reaction mixture was cooled to ambient temperature, the solvent was evaporated *in vacuo* and the residue was triturated with cold methanol to give **17–20**.

One-pot preparation of compound 19

1,2,3,3a,4,5-Hexahydropyrrolo[1,2-*a*]quinoline-4,4-dicarbonitrile (19). A mixture of *ortho*-fluorobenzaldehyde **9** (1 mmol), pyrrolidine (1 mmol) and potassium carbonate (1 mmol) in water (2 mL) was irradiated at 130 °C for 3 min at 50 W maximum power. The reaction mixture was cooled to room temperature, extracted with diethyl ether (3 × 10 mL), washed with a saturated ammonium chloride solution and then with water. The combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated *in vacuo*. The crude aldehyde **12** was suspended in water (3 mL), malononitrile (1 mmol) was added and the reaction mixture was irradiated at 100 °C for 10 min at 60 W maximum power. The vial was cooled down to ambient temperature, TFA (1 drop) was added and the suspension was irradiated at 200 °C for 3 min at 100 W maximum power. The reaction mixture was cooled down to room temperature, extracted with diethyl ether (3 × 10 mL), washed with a saturated ammonium chloride solution and then with water. The combined organic layers were dried over magnesium sulfate, the solvent was evaporated *in vacuo* and the crude product was recrystallized from methanol to give **19** in 50% yield.

1,2,3,3a-Tetrahydro-5*H*-4-oxa-9b-aza-cyclopenta[*a*]naphthalene (21). A mixture of *ortho*-fluorobenzaldehyde **9** (1 mmol), pyrrolidine (1 mmol) and potassium carbonate (1 mmol) in water (2 mL) was irradiated at 130 °C for 3 min at 50 W maximum power and then at 210 °C for 50 min at 110 W maximum power. The reaction mixture was cooled to room temperature, extracted with diethyl ether (3 × 10 mL), washed with a saturated ammonium chloride solution and then with water. The combined organic layers were dried over magnesium sulfate, the solvent was evaporated *in vacuo* and the crude product was purified by column chromatography over silica gel (dichloromethane-*n*-hexane, 1 : 1) to afford **21** in 28% yield. Yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.16 (t, 1H, J = 7.3 Hz), 6.93 (d, 1H, J = 7.3 Hz), 6.75 (t, 1H, J = 7.3 Hz), 6.71 (d, 1H, J = 8 Hz), 4.96 (d, 1H, J = 14.6 Hz), 4.95 (m, 1H), 4.77 (d, 1H, J = 14.6 Hz), 3.62 (m, 1H), 3.27 (m, 1H), 2.35 (m, 1H), 2.01 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 143.6, 128.1, 125.1, 122.0, 118.3, 115.6, 89.9, 68.6, 50.1, 32.8, 23.0. DEPT ($CDCl_3$): 128. 1, 125.1, 118.3, 115.6, 89.9, −68.6, −50.1, −32.8, −23.0 MS (CI): *m*/*z* (%) = 176 (100) [MH^+].

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