Microwave-Assisted Synthesis of Polysubstituted Pyridazines

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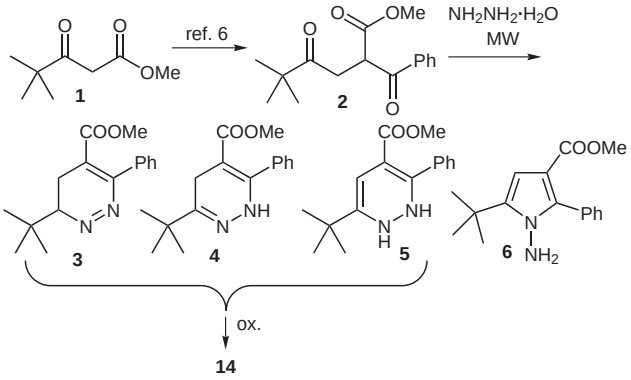
Abstract: 3,4,6-Trisubstituted pyridazines are prepared through a microwave-assisted cyclocondensation of differently substituted 1,4-diketones and hydrazine in the presence of DDQ. The 1,4-diketones can be easily prepared through a functional homologation of commercially available β-keto esters providing a very rapid entry to these family of pharmaceutically important compounds.

Key words: pyridazines, microwaves, cyclocondensation, combinatorial chemistry

Heterocyclic chemistry is nowadays experiencing a renewed interest for the preparation of libraries of drug-like compounds to be submitted to high throughput biological screening.[1] The presence in many natural products and drugs makes heterocycles ideal scaffolds for the preparation of collections of new compounds through elaboration of functionalities present in the substituents. Pyridazines show different interesting pharmacological activities and have inspired several researchers to design new potential therapeutic agents based on this heterocycle.[2] Consequently, syntheses of these compounds have attracted considerable interest[3] especially in the case of synthetic protocols that allow the generation of a high level of diversity.[4] Generally, syntheses of polysubstituted pyridazines are based on nucleophilic substitution on 3- or 6-halopyridazines using different Pd-based chemistry or other organometallic approaches.[5] Although very efficient, these methods limit the possibility of introducing diversity in position 3 or 4.

Recently, we described a convenient procedure to prepare polyfunctionalized 1,4-dicarbonyl compounds based on the functional homologation of β-keto esters with different aldehydes in the presence of Et_2Zn/CH_2I_2.[6] As similar compounds have been described as suitable substrates to prepare pyridazines,[7] we explored the possibility of carrying out a microwave-assisted cyclocondensation to produce a rapid entry to 3,4,6-trisubstituted pyridazines.

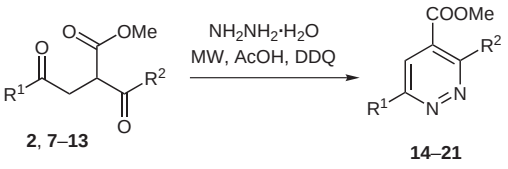
At first, we explored the possibility to cyclize compound **1** with hydrazine under microwave irradiation. Unfortunately, we obtained low yield of the required compound together with different amounts of the 1-amino pyrrole[8] **6** (Scheme 1). Different reaction conditions were tried; best results were obtained carrying out the microwave-assisted cyclocondensation in AcOH at 110 °C for ten minutes.[9]



Scheme 1

The reaction of 1,4-diketones and hydrazine has been reported to afford pyridazines directly.[10] However, we observed that the products obtained in this reaction were a mixture of dihydropyridazines **3**–**5**. Although compounds **3**–**5** could be easily transformed into the corresponding pyridazines using different oxidizing agents,[11] a high-throughput synthesis required the formation of the pyridazine ring in a single step. The keto ester **1** was used as a model compound and we found that, when the reaction was carried out in the presence of 5 equivalents of hydrazine and 1.5 equivalents of DDQ, pyridazine **14** was obtained in 72% yield.

Table 1 Microwave-Assisted Preparation of Pyridazines



Diketone; R^1, R^2	Reaction conditions	Product (yield, %)[a]
2; *t*-Bu, Ph	120 °C, 1.5 min	**14** (60)
7; *t*-Bu, *p*-ClPh	120 °C, 1.5 min	**15** (49)
8; *t*-Bu, $PhCH_2CH_2$	120 °C, 1.5 min	**16** (58)
9; Me, Pr	120 °C, 1.5 min	**17** (48)
10; Et, Pr	120 °C, 3 min	**18** (52)
11; Ph, $PhCH_2$	150 °C, 3 min	**19** (65)
12; Ph, *p*-MeOPh	150 °C, 3 min	**20** (52)
13; Ph, *p*-ClPh	150 °C, 3 min	**21** (54)

[a] Yields of isolated and fully characterized products.

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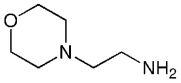
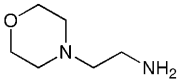
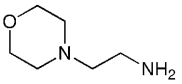
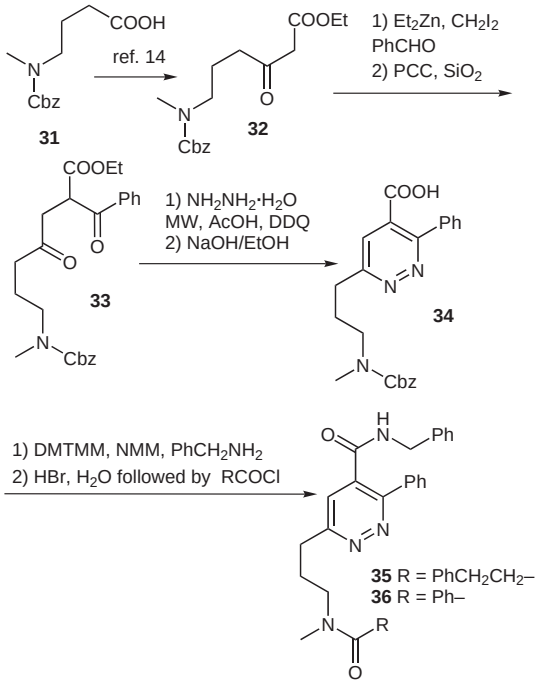
Starting from γ-keto esters **7**–**13**, obtained as described for compound **2**,[6] pyridazines **14**–**21** were obtained in acceptable yield (see Table 1). The molecular diversity at positions 3 and 6 come from the β-keto ester and the aldehyde employed in the functional homologation, while the carboxymethyl group in position 4 could be used for a further increase of diversity. Thus, we tried to carry out a direct amidation of the ester function using primary or secondary amines and $AlMe_3$ without success.[12] Consequently, the carboxymethyl groups of compounds **15**, **16** and **19** (Table 2) were hydrolyzed and the amides **22**–**30** formed by coupling mediated by DMTMM.[13]

Table 2 Pyridazines Amides

Pyridazine ester	Amine	Pyridazine amides (yield, %)[a]
15	$PhCH_2NH_2$	**22** (86)
15	$Me_2CHCH_2NH_2$	**23** (80)
15		**24** (86)
16	$PhCH_2NH_2$	**25** (79)
16	$Me_2CHCH_2NH_2$	**26** (82)
16		**27** (77)
19	$PhCH_2NH_2$	**28** (72)
19	$Me_2CHCH_2NH_2$	**29** (70)
19		**30** (84)

[a] Yields of crude product (calculated on the starting ester) with a purity of at least 90% (NMR analysis).

Finally, the synthetic protocol described here was used to prepare the pyridazine scaffold **34** suitable for double decoration at the side chain in position 6 and in position 4. γ-*N*-Methylaminobutyric acid was protect as Cbz (**31**) and transformed into the β-keto ester **32** with the method of Masamune [carbonyl diimidazole (CDI), CH(COOMe)COOH, $(EtO)_2Mg$].[14] Reaction of **32** with Et_2Zn/CH_2I_2 and benzaldehyde afforded compound **33** that was cyclized under standard conditions to give compound **34** (31% overall yield, Scheme 2). Then we tried to carry out Cbz deprotection using different conditions [H_2, Pd/C or $Pd(OH)_2/C$; transfer hydrogenolysis with Pd/cyclohexadiene or Pd/ammonium formate in different solvents] but in all cases we obtained a compound with a mass spectrum corresponding to the product of partial reduction of the pyridine ring. Thus, the carboxymethyl group was first transformed into the corresponding amide under standard conditions (hydrolysis and coupling as for compounds **22**–**30**) and finally the Cbz group was removed with HBr and the amino group coupled with two acyl chlorides to give products **35** and **36** in 64% and 54% yield, respectively, starting from pyridazine **34**. This last transformation demonstrates the versatility of our synthesis for the application to the preparation of parallel arrays of differently decorated pyridazine scaffolds.



Scheme 2

In conclusion, we have described a new rapid entry to polyfunctionalized pyridazines and to a versatile pyridazine scaffold for parallel synthesis. With this methodology it is possible to prepare various pyridazine with interesting biological activity that will be reported elsewhere.

Methyl 6-*tert*-Butyl-3-(4-chlorophenyl)pyridazine-4-carboxylate (15) – General Procedure

Product **7** (140 mg 0.45 mmol)[6] was dissolved in 0. 35 mL of AcOH in a vial equipped with a stirrer bar and a reflux condenser. Hydrazine hydrate (0.110 mL, 2.25 mmol) and DDQ (0.150 g, 0.68 mmol) were added. The flask was inserted into the cavity of a Discovery Microwave System apparatus (from CEM) and heated at 100 W for 1.5 min (internal temperature and pressure: 120 °C, 250 psi). The solution was diluted with EtOAc, filtered and washed two times with a sat. solution of $NaHCO_3$. The organic layer was dried over anhyd Na_2SO_4 and the solvent evaporated. The crude oil was purified by flash chromatography (PE–EtOAc, 4:1) to obtain the product **15** (60% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.47 (s, 9 H, *t*-Bu), 3.74 (s, 3 H, COOMe), 7.41 (d-like, 2 H, Ar), 7.55 (d-like, 2 H, Ar), 7.74 (s, 1 H, Ar). ES-MS: *m/z* = 305 [M^+ + 1].

Methyl 6-*tert*-Butyl-3-phenylpyridazine-4-carboxylate (14)

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.34 (s, 9 H, *t*-Bu), 3.63 (s, 3 H, COOMe), 7.30–7.34 (m, Ar), 7.44–7.49 (m, Ar). ES-MS: *m/z* = 271 [M^+ + 1].

Methyl 6-*tert*-Butyl-3-(2-phenylethyl)pyridazine-4-carboxylate (16)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, *t*-Bu), 3.15 (t, 2 H, *J* = 6.5 Hz, CH_2), 3.55 (t, 2 H, *J* = 6.5 Hz, CH_2), 3.92 (s, 3 H, COOMe), 7.17–7.27 (m, 5 H, Ar), 7.83 (s, 1 H, Ar). ES-MS: *m/z* = 299 [M^+ + 1], 321 [M^+ + Na].

Methyl 6-Methyl-3-propylpyridazine-4-carboxylate (17)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.97 (t, 3 H, *J* = 7.0 Hz, Me), 1.60–1.83 (m, 2 H, CH_2), 2.71 (s, 3 H, Me), 3.24 (t, 2 H, *J* = 7.0 Hz, CH_2), 3.93 (s, 3 H, COOMe), 7.62 (s, 1 H, Ar). ES-MS: *m/z* = 195 [M^+ + 1], 217 [M^+ + Na].

Methyl 6-Ethyl-3-propylpyridazine-4-carboxylate (18)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.99 (t, 3 H, *J* = 7.0 Hz, Me), 1.37 (t, 3 H, *J* = 7.0 Hz, Me), 1.61–1.86 (m, 2 H, CH_2), 3.03 (q, 2 H, *J* = 7.0 Hz, CH_2), 3.23 (t, 2 H, *J* = 7.0 Hz, CH_2), 3.94 (s, 3 H, COOMe), 7.61 (s, 1 H, Ar). ES-MS: *m/z* = 209 [M^+ + 1], 231 [M^+ + Na].

Methyl 6-Phenyl-3-benzylpyridazine-4-carboxylate (19)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, CH_3), 4.70 (s, 2 H, CH_2), 7.15–7.50 (m, Ar), 8.01–8.11 (m, Ar). ES-MS: *m/z* = 319 [M^+ + 1], 327 [M^+ + Na].

Methyl 6-Phenyl-3-(4-methoxyphenyl)pyridazine-4-carboxylate (20)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OMe), 3.95 (s, 3 H, OMe), 6.97–7.02 (m, Ar), 7.49–7.69 (m, Ar), 8.05 (s, 1 H, Ar), 8.12–8.17 (m, Ar). ES-MS: *m/z* = 321 [M^+ + 1].

Methyl 6-Phenyl-3-(4-chlorophenyl)pyridazine-4-carboxylate (21)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, CH_3), 4.70 (s, 2 H, CH_2), 7.15–7.50 (m, Ar), 8.01–8.11 (m, Ar). ES-MS: *m/z* = 325 [M^+ + 1], 347 [M^+ + Na].

Ethyl 3-Phenyl-6-(3-*N*-methyl-*N*-carbobenzyloxypropyl)pyridazine-4-carboxylate (34)
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.09 (t, 3 H, *J* = 6.9 Hz, Me), 2.10–2.31 (m, 2 H, CH_2), 2.92 (s, 3 H, Me), 2.98–3.11 (m, 2 H, CH_2), 3.41 (t, 2 H, *J* = 6.8 Hz, CH_2), 4.15 (q, 2 H, *J* = 6.9 Hz, CH_2), 5.11 (s, 2 H, CH_2), 7.16–7.35 (m, Ar), 7.40–7.49 (m, Ar), 7.50–7.61 (m, Ar). ES-MS: *m/z* = 434 [M^+ + 1], 456 [M^+ + Na].

6-*tert*-Butyl-*N*-benzyl-3-(4-chlorophenyl)pyridazine-4-carboxamide (22) – General Procedure
Pyridazine **14** (30 mg, 0.094 mmol) was dissolved in 4 mL of a 3:1 EtOH–H_2O solution containing 85 mg of KOH, and the solution was stirred at 90 °C for 4 h. Then, the solution was cooled to r.t. and EtOH evaporated. A solution of 1 N HCl was added and the aqueous layer was extracted three times with EtOAc. The fractions were collected, dried over anhyd Na_2SO_4 and the solvent evaporated. The crude was dissolved into 1 mL of THF and 27 μL of benzylamine (1 equiv), 140 mg of DMTMM (2 equiv), and 75 mg of NMM (3 equiv) were slowly added and the solution was stirred overnight. Then, Et_2O was added and the white precipitate was filtered away. The organic phase was washed two times with a solution of HCl (5%), two times with TEA (10%), two times with HCl (5%) again and finally with brine. The organic layer was dried over anhyd Na_2SO_4 and the solvent was evaporated to give a residue that was purified by flash chromatography ($CHCl_3$–EtOAc–MeOH 4:1:0.5) to give 30 mg of product **22** (yield 66%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (s, 9 H, *t*-Bu), 5.03 (s, 2 H, CH_2), 6.94–6.98 (m, 4 H, Ar), 7.09–7.40 (m, 4 H, Ar), 7.54 (m, 2 H, Ar), 8.06 (br s, 1 H, NH). ES-MS: *m/z* = 380, 382 [M^+ + 1].

Amide 23
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (d, 3 H, *J* = 7.0 Hz, Me), 1.10 (d, 3 H, *J* = 7.0 Hz, Me), 1.18 (s, 9 H, *t*-Bu), 2.23 (m, 1 H, CH), 4.12 (d, 2 H, *J* = 7.0 Hz, CH_2) 7.09–7.40 (m, 5 H, Ar), 8.00 (br s, 1 H, NH). ES-MS: *m/z* = 346, 348 [M^+ + 1].

Amide 24
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (s, 9 H, *t*-Bu), 2.46 (m, 2 H, CH_2), 2.51 (m, 4 H, CH_2), 4.10 (m, 2 H, CH_2), 4.33 (m, 4 H, CH_2) 7.00–7.40 (m, 5 H, Ar), 7.86 (br s, 1 H, NH). ES-MS: *m/z* = 403, 405 [M^+ + 1].

Amide 25
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.14 (s, 9 H, *t*-Bu), 3.10 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.66 (t, *J* = 7.0 Hz, 2 H, CH_2) 5.08 (s, 2 H, CH_2), 7.10–7.40 (m, 11 H, Ar), 8.16 (br s, 1 H, NH). ES-MS: *m/z* = 374 [M^+ + 1].

Amide 26
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.90 (d, 3 H, *J* = 7.0 Hz, Me), 1.08 (d, 3 H, *J* = 7.0 Hz, Me), 1.18 (s, 9 H, *t*-Bu), 2.23 (m, 1 H, CH), 3.10 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.66 (t, *J* = 7.0 Hz, 2 H, CH_2), 4.12 (d, 2 H, *J* = 7.0 Hz, CH_2), 7.20–7.40 (m, 6 H, Ar), 7.76 (br s, 1 H, NH). ES-MS: *m/z* = 340 [M^+ + 1].

Amide 27
^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.15 (s, 9 H, *t*-Bu), 2.46 (m, 2 H, CH_2), 2.51 (m, 4 H, CH_2), 3.10 (t, *J* = 7.0 Hz, 2 H, CH_2), 3.66 (t, *J* = 7 Hz, 2 H, CH_2), 4.10 (m, 2 H, CH_2), 4.33 (m, 4 H, CH_2), 7.10–7.40 (m, 6 H, Ar), 7,59 (br s, 1 H, NH). ES-MS: *m/z* = 397 [M^+ + 1].

Amide 28
^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.60 (s, 2 H, CH_2), 5.18 (s, 2 H, CH_2), 7.00–7.50 (m, 16 H, Ar), 8.00 (br s, 1 H, NH). ES-MS: *m/z* = 380 [M^+ + 1].

Amide 29
^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.92 (d, 3 H, *J* = 7.0 Hz, Me), 1.06 (d, 3 H, *J* = 7.0 Hz, Me), 2.23 (m, 1 H, CH), 3.65 (s, 2 H, CH_2), 4.12 (m, 2 H, CH_2), 7.00–7.50 (m, 11 H, Ar), 8.01 (br s, 1 H, NH). ES-MS: *m/z* = 346 [M^+ + 1].

Amide 29
^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.40 (m, 2 H, CH_2), 2.58 (m, 4 H, CH_2), 3.54 (s, 2 H, CH_2), 4.18 (m, 2 H, CH_2), 4.37 (m, 4 H, CH_2), 7.10–7.40 (m, 11 H, Ar), 7.70 (br s, 1 H, NH). ES-MS: *m/z* = 403 [M^+ + 1].

Butyl 3-Phenyl-6-(3-*N*-methyl–*N*-(2-phenylpropionyl)propyl)pyridazine-4-carboxamide (35)
Compound **24** (200 mg, 0.43 mmol), was stirred at r.t. and 700 μL of a 33% solution of HBr in AcOH were added slowly. After 30 min, $CHCl_3$ (1 mL) was added; the reaction was filtered and washed with a solution of sat. $NaHCO_3$. The aqueous phase was washed three times with $CHCl_3$; the organic layers were collected, washed with brine and dried over anhyd Na_2SO_4. The solvent was removed and the crude was used in the next step. This crude product (80 mg, 0,24 mmol) was dissolved in 5 mL of dry CH_2Cl_2; 40 μL of 3-phenylpropionyl chloride (0.27 mmol), 38 μL of TEA, a catalytic amount of DMAP was added and the solution was stirred at r.t. for 1.5 h. The organic phase was washed with a 1 M solution of HCl and then with brine. The organic layer was dried over anhyd Na_2SO_4 and the solvent was evaporated. The crude oil was purified by flash chromatograpy ($CHCl_3$–EtOAc 4:1) to obtain 70 mg of product **35** (yield 65%).

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.77–0.84 (m, 3 H Me), 1.00–1.39 (m, 4 H, CH_2), 1.72–1.97 (m, 2 H, CH_2), 2.03–2.20 (m, 2 H, CH_2), 2.46–2.65 (m, 2 H, CH_2), 2.83–3.20 (m, 7 H), 3.30–3.41 (m, 4 H, CH_2), 7.07–7.30 (m, Ar), 7.38–7.55 (m, Ar), 7.68–7.75 (m, Ar), 8.00 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 19.8, 25.3, 26.4, 27.3, 29.5, 30.7, 30.8, 31.2, 31.5, 31.7, 32.6, 32.7, 32.3, 34.8, 35.2, 35.3, 39.7, 46.8, 47.0, 49.1, 56.9, 125.3, 125.5, 126.0, 126.1, 126.8, 128.2, 128.3, 128.4, 128.5, 128.9, 129.0, 129.3, 129.5, 133.9, 135.9, 141.0, 141.2, 155.6, 161.0, 161.5, 165.8, 166.1, 172.1, 172.2. ES-MS: *m/z* = 459 [M^+ + 1], 481 [M^+ + Na].

Butyl 3-Phenyl-6-(3-*N*-methyl-*N*-benzoylpropyl)pyridazine-4-carboxamide (36)

Yield 65%. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.73 (t, 3 H, *J* = 7.0 Hz, Me), 0.92–1.26 (m, 4 H, CH_2), 1.98–2.14 (m, 2 H, CH_2), 2.80–3.10 (m, 5 H, CH_2 and Me), 3.35–3.56 (m, 2 H, CH_2), 7.05–7.45 (m, Ar), 7.51–7.63 (m, Ar), 8.00 (d-like, 2 H, Ar), 8.31 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.4, 14.0, 19.7, 20.8, 26.1, 30.6, 32.8, 35.1, 37.4, 39.5, 46.5, 56.8, 60.2, 125.4, 126.6, 128.1, 128.2, 128.3, 128.7, 128.8, 129.2, 129.4, 129.7, 132.6, 134.1, 135.8, 136.1, 136.3, 143.4, 155.7, 161.1, 166.1, 171.4. ES-MS: *m/z* = 431 [M^+ + 1], 453 [M^+ + Na].

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