Synthesis of some novel benzoxazolinonylcarboxamides as potential anti-inflammatory agents

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The synthesis of new 2(3*H*)-benzoxazolinonylcarboxamides starting from 2-amino-4,6-dimethylpyridine and 2(3*H*)-benzoxazolone which were designed as anti-inflammatory agents is described. These derivatives were synthesised from 2(3*H*)-(benzoxazolinon-6-yl)carboxylic acids, which were obtained by Friedel–Crafts acylation of 2(3*H*)-benzoxazolone derivatives with oxalyl chloride and acetylchloride in the presence of the $AlCl_3$–DMF complex. The constitution of the products was supported by elemental analysis IR and ^{1}H NMR spectral data.

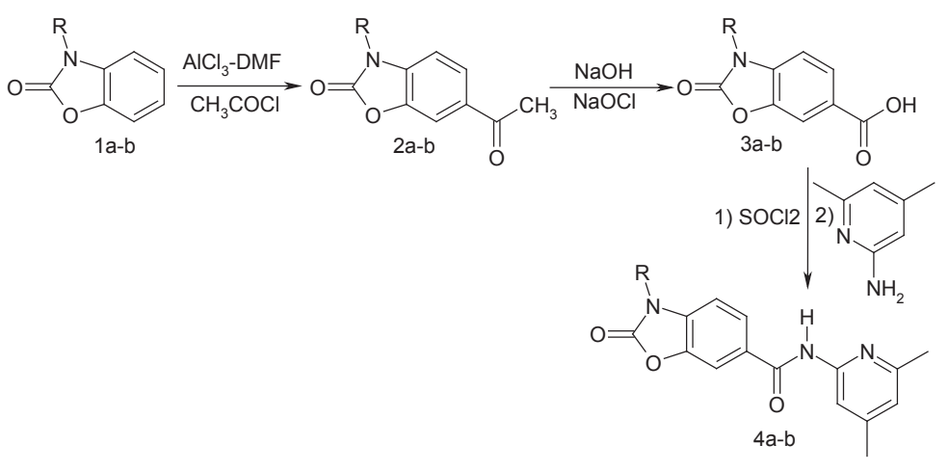
Keywords: carboxamides, 2(3*H*)-benzoxazolone, Friedel–Crafts, acylation, anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) represent one of the most extensively utilised classes of pharmaceutical agents worldwide, and have been used in the treatment of pain, nociception, fever and inflammatory diseases, especially arthritis.[1,2] Since the discovery of an inducible isoform of the enzyme COX later identified as COX-2, in the early 1990s by Needleman, Simmons and Herschman's group,[3–5] numerous COX-2 selective inhibitors have been proposed. Several studies show that the inhibition of cyclooxygenases-2 can delay or prevent certain forms of cancer. In addition to intensive drug discovery programs targeting COX-2 inhibitors, another and perhaps more original approach has been concerned with the exploration of the pharmacological potentials of 2-amino-4,6-dimethylpyridine amide derivatives as mixed inhibitors of both eicosanoid biosynthesis and IL-1/TNF-alpha production.[6] The major compounds in this family are benzamide or phenylacetamide derivatives of 2-amino-4,6-dimethylpyridine.[7–13]

In this connection, we recently reported the synthesis of potentially anti-inflammatory compounds in which the aryl moiety comprised a 2(3*H*)-benzoxazolone ring and n equal to 1.[14] That work was an extension of previous work which our group devoted to anti-inflammatory 6-benzoyl-2(3*H*)-benzoxazolone and 6-benzoyl-2(3*H*)-benzothiazolone derivatives.[15,16] Another merit of this design relies on the creation of a radicalar sensitive centre stabilised by the dipolar arrangement of electron-rich (2(3*H*)-benzoxazolone) and electron-deficient (pyridine) heterocycles placed on either side of the central amide function of the molecule. In an effort to pursue the study of the structure–activity relationships of 2(3*H*)-benzoxazolone analogues, we first considered the importance of the length of alkyl side chain of the benzamides between the aromatic and the amidic portion, and consequently we synthesised carboxamide ($n=0$) instead of acetamide ($n=1$) compounds.[14] In this study, we report the synthesis and characterisation of some novel benzoxazolinonic carboxamide derivatives.

Results and discussion

We now report the preparations of the benzoxazolinonyl-carboxamide derivatives (**4a**, **4b**). The synthesis of the benzoxazolinonylcarboxamides derived from 2-amino-4,6-dimethylpyridine was achieved from 2(3*H)*-benzoxazolone or 3-methyl-2(3H)-benzoxazolone as shown in Scheme 1. It was necessary, however, to develop a good synthesis of the benzoic acid unit. Previous works[17] have shown that this material could be obtained by haloform reaction of the readily available 6-acetyl-2(3*H*)-benzoxazolone (*Method A*). However, the scaling up of this reaction was troublesome. 6-Acetyl-2(3*H*)-benzoxazolone derivatives were obtained as previously reported by taking advantage of the $AlCl_3$–DMF complex used as a Friedel–Crafts catalyst.[18–20] The product of the haloform reaction was hydrolysed in basic medium to give the corresponding acid (**3a**). Treatment of these acids with thionyl chloride gave the intermediate acid chloride which was coupled with 2-amino-4,6-dimethylpyridine to provide the target amide (**4a**).



R=H, CH_3

Scheme 1 Preparation of benzoxazolinonylcarboxamides from (benzoxazolinon-6-yl)carboxylic acids.

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To access to the *N*-methyl derivative acid (R=CH_3, **4b**), we initially planned to use on 3-methyl-2(3*H*)-benzoxazolone in the same procedure described above for the *N*-unsubstituted derivative (**4a**). However, alkaline hydrolysis of the resulting 3-methyl-6-acetyl-2(3*H*)-benzoxazolone (**2b**) resulted in degradation (ring opening) of the heterocycle rather than oxidation of acetyl group. Consequently, we developed a new route based on Friedel–Crafts reaction of 2(3*H*)-benzoxazolone with oxalyl chloride using the $AlCl_3$–DMF complex as catalyst (*Method B*). Indeed, in recent years, our group has developed expertise in the Friedel–Crafts acylation of highly activated substrates using the $AlCl_3$–DMF reagent (Thyes' reagent). We therefore looked for a suitable route for converting an aromatic substrate directly to an aromatic carboxylic acid.[21]

Initial attempts to run the reaction with 2(3*H*)-benzoxazolone as an electron-rich substrate and $AlCl_3$–DMF as catalyst indeed gave the target compound albeit in relatively low yield (33%). Additional trials using 3-methyl-2(3*H*)-benzoxazolone resulted in recoveries of the same order (37%).

In order to achieve the condensation between 2(3*H*)-(benzoxazolinon-6-yl)carboxylic acid or its N-methyl derivative with the 2-amino-4,6-dimethylpyridine to obtain the corresponding amides, these two carboxylic acid derivatives (2(3*H*)-(benzoxazolinon-6-yl)carboxylic acids (**4a–b**) were subjected to three different condensation conditions and tested using different catalysts (*Methods C–E*). The results are reported in Table 1. The proposed structures of the described compounds accord with their IR and ^{1}H NMR spectra.

Table 1 Synthesis of benzoxazolinonic acids (**3a**, **3b**) and carboxamides (**4a**, **4b**)

Compounds	R	M.p./°C	Yield/%[a]	Formula[d]
3a (*Method A,B*)	H	330	90[b], 33[c]	$C_8H_5NO_4$
3b (*Method B*)	CH_3	>250 dec	–, 37[c]	$C_9H_7NO_4$
4a (*Method D,E*)	H	>260	25[e], 63[f]	$C_{15}H_{13}N_3O_3$
4b (*Method D,E*)	CH_3	176–178	47[e], 65[f]	$C_{16}H_{15}N_3O_3$

[a]Pure isolated products; [b]20% NaOH, NaOCl, 1 h; [c]oxalyl chloride $AlCl_3$–DMF, 80 °C, 5 h, see Experimental; [d]dicyclohexylcarbodiimide, anhydrous DMF, room temperature, 24 h; [e]HOBt, EDC, anhydrous DMF and TEA, room temperature, 18 h, see Experimental; [f]Thionyl chloride, $CHCl_3$, reflux, 5 h, see Experimental.

Conclusions

This paper describes the successful synthesis of two derivatives, 2(3*H*)-(benzoxazolinon-6-yl)carboxylic acids, and N-(4,6-dimethylpyridin-2-yl)-2(3*H*)-(benzoxazolinon-6-yl)carboxamide derivatives. Optimisations of the synthesis under three different condensation conditions, using different catalysts were achieved. In conclusion, these results provide useful additions to the design of drugs for the treatment of inflammatory disease.

Experimental

Melting points were determined in open capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. The IR spectra were recorded using potassium bromide disks with a PerkinElmer 297 spectrometer, and wavenumbers are expressed in cm^{-1}. The ^{1}H NMR spectra were recorded using a Brücker AC 300 spectrometer. Chemical shifts (δ) are reported in ppm with tetramethylsilane as internal standard. Elemental analysis was performed by the "Service central d'analyse", CNRS at Solaize Vernaison, France and is within ±0.4% of the calculated values. TLC analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). All the compounds reported here were found chromatographically homogenous in two standard solvents, *i.e.* ethylacetate/cyclohexane (6 : 4, v/v) and methanol/chloroform equilibrated with ammonia (1 : 9, v/v).

FC acylation of 2(3H)-benzoxazolone and 3-methyl-2(3H)-benzoxazolone; general procedure

6-Acetylbenzoxazolinones (**2a**, **2b**) and acid (**3a**, *Method A*) were prepared according to the reported method and the physical properties (m.p., IR, ^{1}H NMR) are in accordance with published data.[17,20]

Synthesis of the 2(3H)-(benzoxazolinon-6-yl) carboxylic acid derivatives (**3a**, **3b**)*; general procedure*

Method B: Anhydrous $AlCl_3$ (13.334 g, 0.10 mol), and under stirring, over 15 min dropwise anhydrous DMF (1.5 mL, 0.02 mol) were added to a 250 mL three-necked flask. When HCl evolution had subsided 2(3*H*)-benzoxazolone (1.351 g, 0.01 mol) was added in one portion. Over a 1 h period oxalyl chloride (1.90 g, 0.015 mol) was added. The temperature of the oil bath was then raised to 80 °C for 5 h, after which time the reaction was poured onto 0.1 kg of ice containing concentrated HCl (3.0 mL). The mixture was allowed to melt under stirring and after 1 h; the precipitate was collected and rinsed with cold distilled water (30.0 mL). The powder so obtained was filtered and recrystallised from suitable solvents to give the desired acids (**3a**) (33%) and (**3b**) (37%).

2(3H)-(Benzoxazolinon-6-yl)carboxylic acid [**3a**, *Method A* (90%) *and Method B* (33%)], m.p. 330 °C. IR (KBr, cm^{-1}): νNH 3140 cm^{-1}, νCO 1775 and 1680 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.17 (d, *J* = 9 Hz, 1H, H4); 7.75 (d, *J* = 1.80 Hz, 1H, H7); 7.83 (m, *J* = 9.0, 1.80 Hz, 1H, H5); 11.97 (br s, 1H, exchanged with D_2O); 12.98 (br s, 1H, exchanged with D_2O). Anal. calcd for $C_8H_5NO_4$: C, 53.64; H, 2.81; N, 7.82; found: C, 53.42; H, 2.96; N, 7.91%.

3-Methyl-2(3H)-(benzoxazolinon-6-yl) carboxylic acid [**3b**, *Method B* (37%)], in the same way as above for 2(3*H*)-(benzoxazolinon-6-yl)carboxylic acid, this material was obtained from methanol, m.p. >250 °C dec. IR: νOH 2400–3100 cm^{-1}, νCH_3 2950 cm^{-1}, νCO 1780 and 1680 cm^{-1}, $\nu C{=}C_{ar}$ 1620 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 3.37 (s, 3H, N–CH_3), 7.35 (d, *J* = 7.89 Hz, 1H, H4), 7.78 (s, 1H, H7), 7.88 (d, *J* = 7.89 Hz, 1H, H5), 13.00 (br s, 1H, exchanged with D2O). Anal. calcd for $C_9H_7NO_4$: C, 55.99; H, 3.65; N, 7.25; found: C, 56.03; H, 3.76; N, 7.34%.

Syntheses of the N-(4,6-dimethylpyridin-2-yl)-2(3H)-(benzoxazolinon-6-yl)carboxamides (**4a**, **4b**)

Method D: A solution of 3-methyl-2(3*H*)-(benzoxazolinon-6-yl) carboxylic acid **3b** (0.59 g, 3 mmol), 2-amino-4,6-dimethylpyridine (0.43 g, 3.6 mmol), HOBt (0.51 g, 3.8 mmol), EDC (0.72 g, 3.8 mmol) in anhydrous DMF (10 mL) and TEA (0.95 mL, 6.8 mmol) was stirred initially at 0 °C for 1 h; it was then allowed to come to room temperature and stirred for additional 18 h after which time the reaction mixture was poured into water (50 mL). The resulting precipitate was recrystallised from 95% ethanol.

Method E: A solution of the appropriate acid **3a** (0.91 g, 5.1 mmol) in chloroform (20 mL) was cooled to 0 °C with stirring. Thionyl chloride (1.75 mL, 24 mmol) was added dropwise, and the reaction mixture was heated at reflux for 5 h. After evaporation, the resulting crude acid chloride was dissolved in dichloromethane (50 mL),to 4 °C, and added dropwise to a cooled mixture of 2-amino-4,6-dimethylpyridine (0.51 g, 4.8 mmol) and triethylamine (0.95 mL, 6.8 mmol) in dichloromethane (50 mL). The reaction mixture was then stirred at room temperature for 18 h. After evaporation of dichloromethane under vacuum, the residue was treated with water and the resulting precipitate filtered, washed with water, dried and recrystallised from 95% ethanol. Compound (**4b**) was synthesised in an identical fashion to (**4a**).

N-(4,6-Dimethylpyridin-2-yl)-2(3H)-(benzoxazolinon-6-yl) carboxamide [**4a**, *Method D* (25%) *and Method E* (63%)], m.p. >260 °C. IR: νNH 3400 and 3392 cm^{-1}, νCO 1772 and 1662 cm^{-1}. ^{1}H NMR (CDCl3) δ 2.30 (s, 3H, –CH_3), 2.40 (s, 3H, –CH_3), 6.87 (s, 1H, H5′), 7.18 (d, *J* = 8.07 Hz, 1H, H4), 7.86 (s, *J* = 0.75 Hz, 1H, H7), 7.90 (dd, *J* = 8.07; *J* = 0.75 Hz, 1H, H5), 7.99 (s, 1H, H3′), 10.60 (br s, 1H, exchanged with

D_2O), 11.00 (br s, 1H, exchanged with D_2O). Anal. calcd for $C_{15}H_{13}N_3O_3$: C, 63.60; H, 4.59; N, 14.84; found: C, 63.80; H, 4.30; N, 14.54%.

3-Methyl-N-(4,6-dimethylpyridin-2-yl)-2(3H)-(benzoxazolinon-6-yl)carboxamide [**4b**, *Method D* (46%) *and Method E* (65%)], m.p. 176–178 °C. IR: νNH 3363, νCO 1778 and 1660 cm^{-1}. ^1H NMR (CDCl3) δ 2.31 (s, 3H, $-CH_3$), 2.41 (s, 3H, $-CH_3$), 3.38 (s, 3H, N–CH_3), 6.89 (s, 1H, H3′), 7.36 (d, J = 7.85 Hz, 1H, H4), 7.64 (m, 2H, H7; H5′), 7.99 (d, J = 7.85 Hz, 1H, H5), 10.60 (br s, 1H, exchanged with D2O). Anal. calcd for $C_{16}H_{15}N_3O_3$: C, 64.61; H, 5.08; N, 14.12; found: C, 64.67; H, 5.05; N, 14.20%.

This work was financially supported by the Algerian Ministry of Higher Education and Scientific Research (MESRS). We thank Prof. D. Lesieur, Institut de Chimie Pharmaceutique, Lille, France, and Prof. Jacques H. Poupaert, Ecole de Pharmacie, Faculté de Médecine, Université Catholique de Louvain, Brussels, Belgium for helpful discussions during the preparation of this manuscript.

Received 19 February 2014; accepted 27 March 2014
Paper 1402476 doi: 10.3184/174751914X13981878697248
Published: 10 June 2014

References

1 J.R. Vane, *Nat. New. Biol.*, 1971, **231**, 232.
2 I.A. Mardini and G.A. FitzGerald, *Mol. Interv.*, 2001, **1**, 30.
3 J.L. Masferrer, B.S. Zweifel, K. Seibert and P. Needleman, *J. Clin. Inves.*, 1990, **86**, 1375.
4 W.L. Xie, J.G. Chipman, D.L. Robertson, R.L. Erikson and D.L. Simmons, *Proc. Natl. Acad. Sci. USA*, 1991, **88**, 2692.
5 D.A. Kujubu and H.R. Herschman, *J. Biol. Chem.*, 1988, **267**, 7991.
6 F. Lang, J.M.H. Robert, P. Boucrot, L. Welin and J.Y. Petit, *J. Pharmacol. Exp. Ther.*, 1995, **275**, 171.
7 S. Robert-Piessard, G. Le Baut, J. Courant, J.D. Brian, L. Sparfel, S. Bouhayat, J.Y. Petit, N. Grimaud and L. Welin, *Eur. J. Med. Chem.*, 1997, **25**, 9.
8 M. Duflos, J. Courant, G. Le Baut, N. Grimaud, P. Renard, D. Manchez and D.H. Caignard, *J. Med. Chem.*, 1998, **33**, 635.
9 K. Fikri, J. Debord, J.C. Bollinger, D. Cledat, B. Penicaut and J.M.H. Robert, *J. Liquid Chromat. Relat. Technol.,* 2011, **34**, 1356.
10 J.M.H. Robert, S. Robert-Piessard, M. Duflos, G. Le Baut, E. Khetteab, N. Grimaud, J.Y. Petit and L. Welin, *Eur. J. Med. Chem.,* 1994, **29**, 841.
11 J.M.H. Robert, S. Robert-Piessard, J. Courant, G. Le Baut, B. Robert, F. Lang, J.Y. Petit, N. Grimaud and L. Welin, *Eur. J. Med. Chem.*, 1995, **30**, 915.
12 J.M.H. Robert, O. Rideau, S. Robert-Piessard, M. Duflos, G. Le Baut, N. Grimaud, M. Juge and J.Y. Petit, *Drug. Res.*, 1997, **47**, 635.
13 J. Debord, P. N'Diaye, J.C. Bollinger, K. Fikri, B. Penicaut, J.M. Robert, S. Robert-Piessard and G. Le Baut, *J. Enzym. Inhib.*, 1997, **12**, 13.
14 M. Liacha, S. Yous, P. Depreux, J.H. Poupaert and D. Lesieur, *Heterocycles*, 1999, **51**, 1929.
15 J.P. Bonte, D. Lesieur, C. Lespagnol, M. Plat, J.C. Cazin and M. Cazin, *Eur. J. Med. Chem.,* 1974, **7**, 491.
16 S. Yous, J.H. Poupaert, I. Lesieur, P. Depreux and D. Lesieur, *J. Org. Chem.*, 1994, **59**, 1574.
17 P. Carato, S. Yous and P. Depreux, *Org. Prep. Proc. Int.*, 2000, **32**, 69.
18 H. Aichaoui, I. Lesieur and J.P. Henichart, *Synthesis*, 1990, **8**, 679.
19 H. Aichaoui, D. Lesieur and J.P. Henichart, *J. Heterocycl. Chem.*, 1992, **29**, 171.
20 M. Liacha, S. Yous, J.H. Poupaert, P. Depreux and H. Aichaoui, (1999) *Monatsh. Chem.*, 1999, **130**, 1393.
21 P.E. Sokol, *Org. Synth.*, 1955, **44**, 69.