Multicomponent Synthesis of Highly Substituted 2-Pyridones

Ana G. Neo,[a] Rosa María Carrillo,[a] Susana Barriga,[a] Edelmiro Momán,[b] Stefano Marcaccini,[c] Carlos F. Marcos*[a]

[a] Laboratorio de Química Orgánica y Bioorgánica, LOBO, Departamento de Química Orgánica, Facultad de Veterinaria, Universidad de Extremadura, 10071 Cáceres, Spain

[b] Centre for Synthesis & Chemical Biology, Department of Pharmaceutical & Medicinal Chemistry, Royal College of Surgeons in Ireland, 123 St. Stephens Green, Dublin 2, Ireland

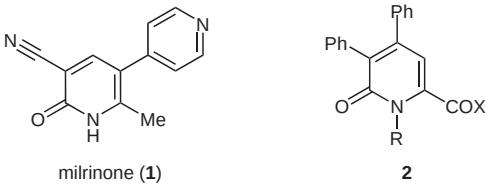
[c] Dipartimento di Chimica Organica 'Ugo Schiff', Università di Firenze, 50019 Sesto Fiorentino FI, Italy
Fax +34(927)257110; E-mail: cfernan@unex.es

Received 14 June 2006

Abstract: A novel synthesis of polyfunctionalised pyridones, structurally related to cardiotonic agent milrinone is described. The procedure consists of an Ugi four-component reaction of 3-formylchromones, followed by a base-promoted ring-opening/ring-closing process. Variation of three of the four components in the Ugi reaction allows access to the final products with a combinatorial distribution of substituents.

Key words: cyclisations, drugs, heterocycles, multicomponent reactions, pyridines

2-Pyridones constitute an important type of heterocycles, which have shown varying biological activities. In particular 2-pyridones containing H-bond acceptor substituents in position 5 constitute a relatively new class of specific phosphodiesterase 3 (PDE3) inhibitors. These compounds have been proposed as an advantageous alternative to classic digitalis glycosides for the acute treatment of congestive heart failure (CHF).[1] In fact, milrinone (**1**; Figure 1) is a 3-cyano-substituted pyridone that has been launched by Sterling Winthrop for the clinical treatment of patients with severe heart failure.[2]



milrinone (**1**) **2**

Figure 1

A number of synthetic methods for the preparation of 2-pyridones have been reported,[3] and some of them have been used to obtain milrinone analogues with improved activity.[4] Particularly, 2-oxo-3-pyridinecarbonitriles having a carbonyl moiety at the 5-position exhibited a significant ionotropic activity. However, flexible syntheses of polyfunctionalised 2-pyridones from easily available starting materials are still required.

As part of our studies on the synthetic utility of multicomponent reactions, we have reported a two-step synthesis of 6-carboxamido-2-pyridones **2** (Figure 1).[5] Recently, Beck and co-workers have also reported a synthesis of 2-pyridones based on an Ugi four-component condensation.[6] Now we describe a new multicomponent strategy for the synthesis of 5-aroyl-2-pyridone derivatives **8** related to milrinone.

We envisaged that formylchromones **3** could be transformed to 5-aroyl-2-pyridones **8** through an Ugi reaction, followed by an intramolecular cyclisation, with concomitant opening of the pyranone ring of the chromone (Scheme 1). In the past we have successfully applied similar ring-switching strategies for the synthesis of other heterocyclic systems.[7]

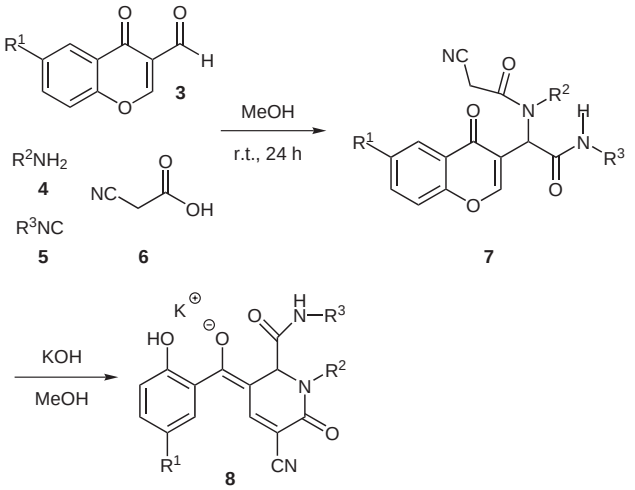
Recently, the synthesis of 5-(2-hydroxybenzoyl)-2-oxo-1,2-dihydropyridine-3-carbonitriles by the reaction of cyanoacetamide with 3-formylchromones has been reported.[8] A limitation of this method is the impossibility of introducing substituents in position 6 of the pyridine nucleus. Substituents in this position could be useful in structure-activity relationship (SAR) studies. Furthermore, they may be important to enhance the PDE3A inhibition (the principal mechanism of action of milrinone analogues) and reduce a secondary activity related to antagonism towards endogenous adenosine at the A_1 receptor.[4c] We think that an amide group in position 6 could provide an extra H-bond with PDE3A Gln331, which is a conserved residue in the superfamily of PDEs, essential for the binding of inhibitors to the active site.[9] Cyclisation of Ugi adducts **7** would directly give 2-pyridones with an amide substituent in the desired position.

Accordingly, we performed the reaction between 3-formylchromone (**3**, R^1 = H), aniline (**4**, R^2 = Ph), cyclohexyl isocyanide (**5**, R^3 = *c*-C_6H_{11}) and cyanoacetic acid (**6**), by simply combining the four components in methanol solution.[10] Stirring the mixture at room temperature readily led to the formation of a precipitate of the expected Ugi four-component adduct **7a**, which was isolated essentially pure in a 67% yield.[11]

Subsequent treatment of **7a** with potassium hydroxide in methanol[12] resulted in the immediate formation of an orange precipitate, which was filtered and identified as the potassium enolate **8a**.[13] As anticipated, the base promoted

SYNLETT 2007, No. 2, pp 0327–0329
Advanced online publication: 24.01.2007
DOI: 10.1055/s-2007-967992; Art ID: D17006ST

an intramolecular addition–elimination reaction of the methylene alpha to the nitrile group onto the chromone endocyclic double bond. Consequently the six-membered pyranone ring was opened and a new pyridone ring was formed (Scheme 1).



Scheme 1

In order to study the scope of the method, we applied the same procedure to different formylchromones **3**, amines **4** and isocyanides **5** (Table 1).[10,12] The Ugi condensation accommodates a variety of aliphatic and aromatic isocyanides and aromatic amines. However, electron-deficient anilines form electrophilic Schiff bases with formylchromone, which suffer conjugate addition of a solvent molecule. The resulting stable enamine **9** (Figure 2)[14] does not react further with the isocyanide and the carboxylic acid. The addition of methanol, though, seems to be reversible, as the methoxy group in **9** is exchanged with an ethoxy group when the enamines are heated in ethanol. Although Ugi reactions are normally favoured in protic solvents, we explored the use of non-nucleophilic solvents in order to avoid the undesired formation of enamine **9**. For example, good results could be obtained for *p*-chloroaniline (Table 1, entry **d**) using toluene in the presence of ammonium chloride.[15,16]

The Ugi adducts usually precipitate from the reaction medium, and can be isolated by simple filtration in moderate to good yields and high degree of purity.[11] After base-promoted cyclisation, pyridones were isolated, also in high yields and purity, as the corresponding potassium enolates **8**, which precipitate as easily filterable yellow-orange solids. The enolates have been characterized in their ionic form, and their IR, ^{1}H NMR, ^{13}C NMR, MS and ACC–MS spectroscopic data are in agreement with the proposed structure.[13] Table 1 summarises the results of the Ugi and cyclisation reactions.

As different 3-formylchromones **3**, amines **4** and isocyanides **5** are easily available; a wide variety of substituents can be introduced on the salicyl ring, on the pyridone

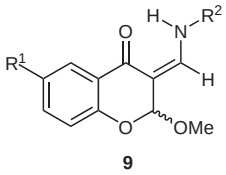


Figure 2

nitrogen, and, more importantly, on the amide group at position 6. On the other hand, pyridone carbon-4 remains unsubstituted, as in all active milrinone analogues reported in the literature.

In summary, we have developed a practical method that allows access, in just two reaction steps, to highly functionalised pyridines with a variety of substituents. The experimental simplicity of this method and the possibility to isolate both the intermediates and the final products by simple filtration, with a reasonable grade of purity, makes it suitable for combinatorial synthesis. This strategy could be easily applied to the synthesis of libraries of analogues of the inotropic/vasodilator agent milrinone.

Table 1 Results of the Ugi and Cyclisation Steps in the Synthesis of 2-Pyridone Derivatives

	R^1	R^2	R^3	Yield of **7** (%)[a]	Yield of **8** (%)[b]
a	H	Ph	*c*-C_6H_{11}	67	75
b	H	4-MeC_6H_4	*c*-C_6H_{11}	49	75
c	H	4-FC_6H_4	*c*-C_6H_{11}	68	84
d	H	4-ClC_6H_4	*c*-C_6H_{11}	48[c]	58
e	H	Ph	*t*-Bu	63	51
f	H	4-MeC_6H_4	*t*-Bu	47	79
g	H	4-FC_6H_4	*t*-Bu	54	59
h	H	Ph	C_5H_{11}	55	57
i	H	4-FC_6H_4	C_5H_{11}	55	22
j	H	4-FC_6H_4	2,6-$Me_2C_6H_3$	27	61
k	Me	Ph	*c*-C_6H_{11}	50	62
l	Me	Ph	*t*-Bu	45	62

[a] Experimental procedure and representative data are given in refs. 10 and 11.
[b] Experimental procedure and representative data are given in refs. 12 and 13.
[c] Experimental procedure is described in ref. 16.

Acknowledgment

We thank Consejería de Educación Ciencia y Tecnología of Junta de Extremadura and FEDER (2PR04A003 & 3PR05C022) for the financial support.

References and Notes

(1) Dorigo, P.; Gaion, R. M.; Belluco, P.; Fraccarollo, D.; Maragno, I.; Bombieri, G.; Benetollo, F.; Mosti, L.; Orsini, F. *J. Med. Chem.* **1993**, *36*, 2475.

(2) Information obtained from the Investigational Drugs Database (IDDB, www.iddb3.com).

(3) For recent examples, see: (a) Chen, Y. H.; Zhang, H. J.; Nan, F. J. *J. Comb. Chem.* **2004**, *6*, 684. (b) Hachiya, L.; Ogura, K.; Shimizu, M. *Synthesis* **2004**, 1349; and the references therein.

(4) See, for example: (a) Fossa, P.; Menozzi, G.; Dorigo, P.; Floreani, M.; Mosti, L. *Bioorg. Med. Chem.* **2003**, *11*, 4749. (b) Altomare, C.; Cellamare, S.; Summo, L.; Fossa, P.; Mosti, L.; Carotti, A. *Bioorg. Med. Chem.* **2000**, *8*, 909. (c) Dorigo, P.; Fraccarollo, D.; Gaion, R. M.; Santostasi, G.; Borea, P. A.; Floreani, M.; Mosti, L.; Maragno, I. *Gen. Pharmacol.* **1997**, *28*, 781. (d) Mosti, L.; Schenone, P.; Iester, M.; Dorigo, P.; Gaion, R. M.; Fraccarollo, D. *Eur. J. Med. Chem.* **1993**, *28*, 853.

(5) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Heterocycles* **1997**, *45*, 1589.

(6) Beck, B.; Picard, A.; Herdtweck, E.; Dömling, A. *Org. Lett.* **2004**, *6*, 39.

(7) (a) Marcaccini, S.; Pepino, R.; Marcos, C. F.; Polo, C.; Torroba, T. *J. Heterocycl. Chem.* **2000**, *37*, 1501. (b) Bossio, R.; Marcos, C. F.; Marcaccini, S.; Pepino, R. *Synthesis* **1997**, 1389.

(8) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Tolmachev, A. A. *Synlett* **2004**, 2287.

(9) Jeon, Y. H.; Heo, Y. S.; Kim, C. M.; Hyun, Y. L.; Lee, T. G.; Ro, S.; Cho, J. M. *CMLS, Cell. Mol. Life Sci.* **2005**, *62*, 1198.

(10) **Synthesis of the Ugi adducts (7): General Procedure for Method A**: 3-Formylchromone (**3**; R^1 = H) or 6-methyl-2-formylchromone (**3**; R^1 = CH_3, 5 mmol) was dissolved in MeOH (5 mL). Amine **4** (5 mmol) was added, and the mixture was stirred for 15 min at r.t. Isocyanide **5** (5 mmol) and cyanoacetic acid (**6**; 5 mmol) were successively added and the mixture was stirred for 24–48 h at r.t. An abundant precipitate was formed, which was filtered and successively washed with *i*-PrOH and *i*-Pr_2O, yielding a product pure enough to be used in the following reaction. For analytical purposes it may be further purified by recrystallisation from EtOH.

(11) **Representative Data: 2-Cyano-*N*-[cyclohexylcarbamoyl(4-oxo-4*H*-chromen-3-yl)methyl]-*N*-phenylacetamide (7a)**: Yield: 67%; white solid; mp 217–218 °C. IR: 3336, 2931, 2360, 1650, 1543, 1466, 761 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.1 Hz, 1 H), 8.03 (s, 1 H), 7.64 (t, *J* = 7.1 Hz, 1 H), 7.03–7.60 (m, 7 H), 6.47 (d, *J* = 8.4 Hz, 1 H), 6.31 (s, 1 H), 3.76–3.83 (m, 1 H), 3.33 (d, *J* = 18.5 Hz, 1 H), 3.17 (d, *J* = 18.5 Hz, 1 H,), 1.13–2.02 (m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.83 (C), 167.79 (C), 162.88 (C), 158.06 (CH), 155.75 (C), 138.34 (C), 134.03 (CH), 129.78 (CH), 129.51 (CH), 125.84 (CH), 125.57 (CH), 123.30 (C), 118.17 (CH), 117.93 (C), 113.81 (C), 55.84 (CH), 48.98 (CH), 32.66 (CH_2), 26.51 (CH_2), 25.39 (CH_2), 24.72 (CH_2). MS (EI): *m*/*z* (%) = 444 (<1) [M^+ + 1], 318 (12), 250 (100), 172 (3), 130 (5), 77 (2). HRMS: *m*/*z* calcd for $C_{26}H_{25}N_3O_4$: 443.1849; found: 443.1845.

(12) **Cyclisation of the Ugi Adducts (7): General Procedure**: A 0.5 M solution of KOH in EtOH (1 mL, 0.5 mmol) was added to a solution of the Ugi adduct (**7**, 0.5 mmol) in EtOH (1 mL). The mixture was stirred for 8 h at r.t. and the orange-yellow precipitate obtained was filtered and washed with *i*-Pr_2O, yielding compound **8** in an essentially pure form.

(13) **Representative Data for Potassium 5-Cyano-2-cyclohexylcarbamoyl-6-oxo-1-phenyl-1,6-dihydro-2*H*-pyridin-3-ylidene(2-hydroxyphenyl)methanolate (8a)**: Yield: 75%; orange solid; mp 275 °C (dec.). IR: 3439, 2928, 2194, 1679, 1607, 1554, 1520, 1240, 771 cm^{-1}. ^1H NMR (400 MHz, DMSO): δ = 10.66 (s, 1 H), 7.56 (d, *J* = 8.1 Hz, 1 H), 7.31 (t, *J* = 8.0 Hz, 2 H), 7.23 (t, *J* = 7.1 Hz, 2 H), 7.11–7.19 (m, 3 H), 7.06 (s, 1 H), 6.86 (s, 1 H), 6.84 (s, 1 H), 5.28 (s, 1 H), 3.47–3.55 (m, 1 H), 1.04–1.75 (m, 10 H). ^{13}C NMR (100 MHz, DMSO): δ = 183.28 (C), 169.91 (C), 164.31 (C), 156.83 (C), 147.65 (CH), 143.47 (C), 130.64 (CH), 129.59 (CH), 128.30 (CH), 125.68 (CH), 125.24 (C), 124.91 (CH), 122.21 (C), 118.34 (CH), 116.33 (CH), 105.83 (C), 78.28 (C), 62.07 (CH), 47.03 (CH), 32.34 (CH_2), 31.93 (CH_2), 25.42 (CH_2), 25.23 (CH_2), 23.85 (CH_2). MS (FAB): *m*/*z* (%) = 520 (100) [M^+ + K], 482 (96) [M^+ +1], 444 (18), 376 (29), 356 (19), 355 (72), 338 (62), 317 (29). HRMS (FAB): *m*/*z* calcd for $C_{26}H_{25}KN_3O_4$: 482.1482; found: 482.1487.

(14) Enamines **9** were identified by ^1H NMR and ^{13}C NMR as the major products obtained in the reactions with 4-chloroaniline, 3,5-dichloroaniline, 4-nitroaniline and 1-aminonaphthalene. For example ^1H NMR data of (*Z*)-3-[(4-chlorophenylamino)methylene]-2,3-dihydro-2-methoxychromen-4-one (**9**; R^1 = H, R^2 = 4-ClC_6H_4), obtained from 4-chloroaniline and 3-formylchromone, was identical to the published data: (a) Fitton, A. O.; Frost, J. R.; Suschitzky, H. *Tetrahedron Lett.* **1975**, *16*, 2099. (b) Fitton, A. O.; Frost, J. R.; Houghton, P. G.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1691.

(15) Cristau, P.; Vors, J. P.; Zhu, J. *Tetrahedron* **2003**, *59*, 7859.

(16) **Synthesis of the Ugi Adducts; Method B**: Equimolar amounts of the four components and NH_4Cl were stirred in toluene for 48 h at r.t. The resulting precipitate was filtered and successively washed with *i*-PrOH and hexanes.