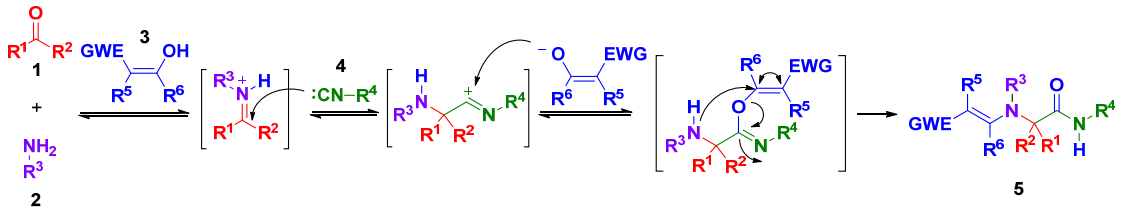
Enol-Ugi Reaction for the Synthesis of Amino Acid Derived Coumarins

Ana G. Neo,* Teresa G. Castellano, Carlos F. Marcos*

Laboratory of Bioorganic Chemistry & Membrane Biophysics, School of Veterinary Sciences, University of Extremadura, 10071 Cáceres, Spain
E-mail: cfernan@unex.es, aneo@unex.es

Introduction

The Ugi condensation[1] [2] is a multicomponent reaction of isocyanides, MCRIs, in which carboxylic acids, carbonyl compounds, amines and isocyanides react to give diversely functionalised α-acylamino amides. The wide functional group tolerance of this type of reaction permits to achieve additional structural variety through post-condensation transformations. [3] The replacement of one of the four components by a new reagent with similar reactivity and chemical behavior constitutes a potent approach to attain scaffold diversity employing Ugi type reactions. This strategy was previously used by Ugi himself, and has been recently coined by Ganem as *single reactant replacement* (SRR).[4] We have demonstrated[5] that enols [6] can react in one-pot with carbonyl compounds (**1**), amines (**2**) and isocyanides (**4**) to give amino acid-derived enamines in a so called enol-Ugi condensation (**5**; *Scheme 1*). A structural requirement for the enol is the presence of at least one α,β-unsaturated electron-withdrawing group, which facilitates a conjugate addition-β-elimination rearrangement on the primary adduct, leading to a stable product.



Scheme 1. Mecanism of the enol-Ugi reaction

The coumarin system is present in a large family of plant metabolites with important biological activities. In particular, 3- and 4-aminocoumarins are presents in the structural core of numerous pharmaceuticals. For example, 4-aminocoumarins have shown potent antimicrobial,[7] antiproliferative,[8] cytotoxic[9] and anthrax inhibitory[10] activities. Natural 3-aminocoumarin antibiotics, such as novobiocin, clorobiocin and coumermycin, are known DNA gyrase inhibitors.[11] Analogues of novobiocin are nsp90 inhibitors and present anti-proliferative activity.[12] Other 3-aminocoumarins derivatives present biological activity, including bactericidal[13] and monoamino oxidase (MAO) and acetylcholinesterase (AChE) inhibitory activities[14]. Also, aminocoumarin derivatives present interesting photochemical properties and have found application as fluorescent markers.[15] The introduction of complex aminoacyl substituents in the position 3 or 4 of coumarins would afford an effective strategy to control the physical or biological properties of these coumarin derivatives.

Here we wish to report the synthesis of 3- and 4-aminocoumarins by an enol-Ugi condensation using 3- and 4-hydoroxycoumarins, imines and isocyanides.

Results

To satisfy the structural requirements of the starting enols, it was necessary to introduce an electron-withdrawing group into the 3-position of 4-hydroxycoumarine or into the 4-position of 4-hydroxycoumarine.

Thus, we prepared, in the first place, 4-hydroxycoumarins containing different electron-withdrawing groups in the position 3, *Figure 1*, and we tested these compounds in the projected enol-Ugi type reaction.

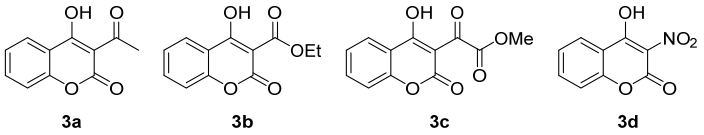
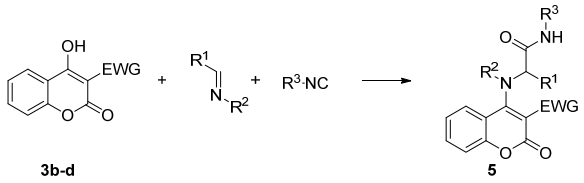


Figure 1. 3-Substituted 4-hydroxycoumarins used in enol-Ugi reactions

Accordingly, equimolar amounts of 4-hydroxycumarin derivatives, cyclohexyl isocyanide and imines were mixed in different reaction conditions. Except for the enol **3a**, which do not react under any of the tested conditions, in all of the other cases the reaction takes place at 25 ºC affording the corresponding enol-Ugi product, *Table 1*.

Table 1. Enol-Ugi reactions of 4-hyroxycoumarin derivatives

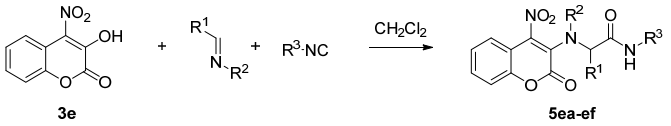


Entry	Enol	R^1	R^2	R^3	Solvent	5 (%)
1	**3b**	C_6H_5	$C_6H_5CH_2$	*c*C_6H_{11}	*i*PrOH	**ba** (63)
2	**3b**	C_6H_5	$C_6H_5CH_2$	*t*Bu	*i*PrOH	**bb** (60)
3	**3b**	C_6H_5	$C_6H_5CH_2$	2,6Me_2Ph	*i*PrOH	**bc** (43)
4	**3b**	C_6H_5	$C_6H_5CH_2$	CH_2CO_2*t*Bu	*i*PrOH	**bd** (42)
5	**3b**	C_6H_5	3,4-(OCH_2O)Bn	*c*C_6H_{11}	*i*PrOH	**be** (65)
6	**3b**	2-furyl	$C_6H_5CH_2$	*c*C_6H_{11}	*i*PrOH	**bf** (27)
7	**3b**	C_6H_5	C_6H_5	*c*C_6H_{11}	*i*PrOH	**bg** (62)
8	**3b**	C_6H_5	C_6H_5	2,6Me_2Ph	*i*PrOH	**bh** (47)
9	**3c**	C_6H_5	C_6H_5	*c*C_6H_{11}	*i*PrOH	**ca** (64)
10	**3c**	C_6H_5	C_6H_5	*t*Bu	*i*PrOH	**cb** (39)
11	**3c**	*p*-Me-C_6H_4	C_6H_5	*c*C_6H_{11}	*i*PrOH	**cc** (60)
12	**3c**	*p*-Me-C_6H_4	C_6H_5	CH_2Ph	*i*PrOH	**cd** (87)
13	**3c**	C_6H_5	$C_6H_5CH_2$	*c*C_6H_{11}	*i*PrOH	**ce** (63)
14	**3c**	C_6H_5	$C_6H_5CH_2$	*t*Bu	*i*PrOH	**cf** (49)
15	**3c**	C_6H_5	3,4-(OCH_2O)Bn	*c*C_6H_{11}	CH_2Cl_2	**cg** (61)
16	**3d**	C_6H_5	$C_6H_5CH_2$	*c*C_6H_{11}	CH_2Cl_2	**da** (95)
17	**3d**	C_6H_5	$C_6H_5CH_2$	*t*Bu	CH_2Cl_2	**db** (63)
18	**3d**	C_6H_5	C_6H_5	*c*C_6H_{11}	CH_2Cl_2	**dc** (63)
19	**3d**	C_6H_5	C_6H_5	*t*Bu	CH_2Cl_2	**dd** (42)
20	**3d**	C_6H_5	C_6H_5	2,6Me_2Ph	CH_2Cl_2	**de** (66)

21	**3d**	*p*-F-C_6H_4	C_6H_5	*c*C_6H_{11}	CH_2Cl_2	**df** (48)
22	**3d**	*p*-Me-C_6H_4	C_6H_5	*c*C_6H_{11}	CH_2Cl_2	**dg** (65)
23	**3d**	*p*-Me-C_6H_4	C_6H_5	*t*Bu	CH_2Cl_2	**dh** (44)

Furthermore, we prepared 3-hydroxy-4-nitrocoumarin[6], which reacts under the same conditions that its isomeric enol of **3d**, yielding the enol-Ugi products **5ea-5ef** in good yields, *Table 2*.

Table 2. Enol-Ugi reactions of 3-hydroxy-4-nitrocoumarin



Entry	R^1	R^2	R^3	5 (%)
1	C_6H_5	$C_6H_5CH_2$	*c*C_6H_{11}	**ea** (78)
2	C_6H_5	3,4-(OCH_2O)Bn	*c*C_6H_{11}	**eb** (59)
3	C_6H_5	C_6H_5	*c*C_6H_{11}	**ec** (78)
4	C_6H_5	C_6H_5	*t*Bu	**ed** (64)
5	C_6H_5	C_6H_5	2,6Me_2Ph	**ee** (73)
6	*p*-Me-C_6H_4	C_6H_5	*t*Bu	**ef** (67)

Conclusions

We have prepared different coumarin enamines containing α-amino amide substituents on position 3 or 4 by the new enol-Ugi condensation of imines, isocyanides and hydroxycoumarins. The wide availability of starting materials and the efficiency versatility of the process also makes it suitable for the combinatorial synthesis of chemical libraries.

Experimental

General procedure for the synthesis of enol adducts. A mixture of imine (0.5 mmol), isocyanide (0.5 mmol) and enol **3** (0.5 mmol) in the indicated solvent (1 mL) was stirred at 25-30 ºC during 48-96 h for the reactions in *i*PrOH or 2-3 h for the reactions in CH_2Cl_2. In the case a precipitate was formed (reactions in *i*PrOH), the reaction mixture was cooled to 0 ºC and the precipitate was filtered and washed with hexanes, yielding the pure products **5ba-5bh**, **5ca-5cf**. In some cases (**5ba-5bh**) a second portion of product was obtained from the filtrate, by adding HCl 10% and H_2O, extracting the resulting mixture with CH_2Cl_2 and purifying the dried extract by column chromatography (SiO_2, hexanes to hexanes-AcOEt 7:3 gradient). For the reactions performed in CH_2Cl_2, the solvent was eliminated and the residue was purified by column chromatography (SiO_2, hexanes to hexanes-AcOEt 7:3 gradient) to give **5cg-5ef**.

Data of Methyl 2-(4-((2-(benzylamino)-2-oxo-1-(*p*-tolyl)ethyl)(phenyl)amino)-2-oxo-2*H*-chromen-3-yl)-2-oxoacetate (5cd):[5c] red solid; m.p.: 119-121 ºC; ^{1}H RMN (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 5.7 Hz, 1H), 7.55 (t, J = 9.63 Hz, 1H), 7.37 – 7.15 (m, 7H), 7.15 – 7.03 (m, 3H), 6.98 (t, J = 7.3 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 7.9 Hz, 2H), 5.65 (s, 1H), 4.53 (d, J = 5.9 Hz, 1H), 4.49 (d, J = 6.0 Hz, 1H), 3.85 (s, 3H), 2.21 (s, 3H) ppm; ^{13}C RMN (101 MHz, $CDCl_3$) δ 184.13, 169.97, 162.70, 160.98, 160.60, 154.42, 145.41, 139.37, 138.02, 134.62, 130.05, 129.76, 129.69, 129.33, 128.73, 128.69, 127.81, 127.47,

125.07, 122.60, 119.85, 117.89, 117.48, 70.77, 53.35, 43.82, 21.28 ppm; HRMS (qTOF) Calcd for $C_{34}H_{29}N_2O_6$: 561.2026. Found: 561.2021.

Data of *N*-(*tert*-Butyl)-2-((4-nitro-2-oxo-2*H*-chromen-3-yl)(phenyl)amino)-2-phenylacetamide (5ed):[5b] red solid; m.p.: 167-169 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 6.69 (m, 15H), 5.41 (s, 1H), 1.29 (s, 9H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.84, 160.37, 156.36, 152.49, 145.40, 133.88, 133.46, 130.50, 129.60, 129.50, 128.80, 125.95 (CH), 123.71 (CH), 123.20 (C), 122.50, 117.56, 116.67, 111.53, 70.41, 51.51, 28.49 ppm; MS (CI) m/z (%) 472 (M+. + 1, 7), 162 (100); HRMS (CI) Calcd for $C_{27}H_{26}N_3O_5$: 472.1877. Found: 472.1872.

Acknowledgements

We thank the financial support from Junta de Extremadura and FEDER.

References

[1] I. Ugi, C. Steinbruckner, *Angew. Chem. Int. Ed. Engl.* **1960**, *72*, 267.
[2] I. Ugi, R. Meyr, U. Fetzer, C. Steinbrückner, *Angew. Chem.* **1959**, *71*, 386.
[3] A. Domling, W. Wang, K. Wang, *Chem. Rev.* **2012**, *112*, 3083.
[4] B. Ganem, *Acc Chem Res* **2009**, *42*, 463.
[5] a)T. G. Castellano, A. G. Neo, S. Marcaccini, C. F. Marcos, *Org. Lett.* **2012**, *14*, 6218; b)A. Neo, T. Castellano, C. Marcos, *Synthesis* **2015**, *47*, 2431; c)A. G. Neo, T. G. Castellano, C. F. Marcos, *Arkivoc* **2016**, *2017*, 21.
[6] G. Wang, H. W. Chen, Y. Oktay, J. Zhang, E. L. Allen, G. M. Smith, K. C. Fan, J. S. Hong, S. W. French, J. M. McCaffery, R. N. Lightowlers, H. C. Morse, 3rd, C. M. Koehler, M. A. Teitell, *Cell* **2010**, *142*, 456.
[7] B. R. Dekic, N. S. Radulovic, V. S. Dekic, R. D. Vukicevic, R. M. Palic, *Molecules* **2010**, *15*, 2246.
[8] M. Di Braccio, G. Grossi, G. Roma, C. Marzano, F. Baccichetti, M. Simonato, F. Bordin, *Il Farmaco* **2003**, *58*, 1083.
[9] Y. Dong, K. Nakagawa-Goto, C.-Y. Lai, S. L. Morris-Natschke, K. F. Bastow, K.-H. Lee, *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4085.
[10] G. Roma, M. D. Braccio, A. Carrieri, G. Grossi, G. Leoncini, M. Grazia Signorello, A. Carotti, *Bioorg. Med. Chem.* **2003**, *11*, 123.
[11] M. Gellert, M. H. O'Dea, T. Itoh, J. Tomizawa, *Proc. Nat. Acad. Sci. USA* **1976**, *73*, 4474.
[12] G. Le Bras, C. Radanyi, J.-F. Peyrat, J.-D. Brion, M. Alami, V. Marsaud, B. Stella, J.-M. Renoir, *J. Med. Chem.* **2007**, *50*, 6189.
[13] A. M. El-Naggar, F. S. M. Ahmed, A. M. A. El-Salam, M. A. Radi, M. S. A. Latif, *Journal of Heterocyclic Chemistry* **1981**, *18*, 1203.
[14] D. Viña, M. J. Matos, M. Yáñez, L. Santana, E. Uriarte, *Med. Chem. Commun.* **2012**, *3*, 213.
[15] A. S. Abreu, B. F. C. Hermenegildo, P. M. T. Ferreira, M. J. R. P. Queiroz, E. M. S. Castanheira, *RSC Advances* **2016**, *6*, 72141.