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Sequential Five-Component Synthesis of Spiropyrrolidinochromanones

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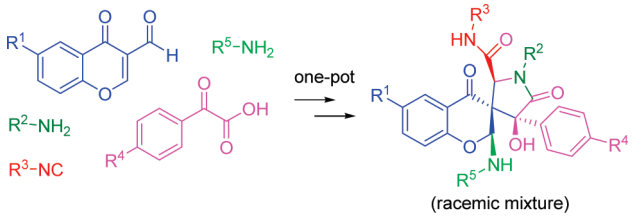

Herein we report a novel, diastereoselective, one-pot, two-step, sequential synthesis of highly functionalized natural product-like spiropyrrolidinochromanones. The process consists of an Ugi four-component condensation of 3-formylchromones with amines, isocyanides, and glyoxylic acids followed by a nucleophilic conjugate addition and intramolecular cyclization. The experimental simplicity and tolerance to a wide variety of substituents makes this method suitable for combinatorial synthesis.

Spiroheterocyclic structures are common scaffolds of many bioactive natural products, including oxindole alkaloids,[1] shellfish toxins,[2] and bioactive marine macrolides.[3] All these molecules incorporate at least two spiro-fused biologically privileged heterocyclic rings[4] disposed in a rigid geometry defined by the spiro motif. This three-dimensional arrangement is crucial in the interaction with biological receptors. Hence, the synthesis of spiranes incorporating two privileged heterocycles could be a valuable strategy to discover new bioactive compounds in the context of chemical genomics.

Benzopyrans and pyrrolidinones have been recognized as two prominent types of privileged structures, which have shown to interact with a variety of biological receptors. The benzopyrane ring system is central to important classes of bioactive natural products as coumarins, chromones, and flavonoids. Some of them contain spiro-fused structures, such as cytotoxic rotenoid amorphispironone,[5] antimalarial robustadials,[6] and antileishmanial euglobals[7] from *Eucalyptus*, and the biflavonoids daphnodorins and genkwanol, isolated from *Daphne* species.[8] Synthetic spirobenzopyranes, such as sorbinil[9] and SNK-860,[10] have been shown to be potent aldose reductase inhibitors and, hence, potentially useful to prevent long-term diabetic complications. On the other hand, the spiropyrrolidine motif is common to most oxindole alkaloids, many of which show singular biological activities. Antitumor agents vinblastine and vincristine[11] and cell cycle regulating spirotryprostatins are representative examples.[12] Other spiropyrrolidines with relevant biological activities include nicotinic receptor blockers,[13] matrix metalloprotease inhibitors,[14] and frog and millipede poisons.[15]

Moreover, spiropyrrolidinochromanones have been already recognized as biologically relevant synthetic targets. However, their synthesis is limited to the 1,3-dipolar cycloaddition reaction of azomethine ylides with 3-methylenechroman-4-ones,[16] a strategy that allows a limited variety of

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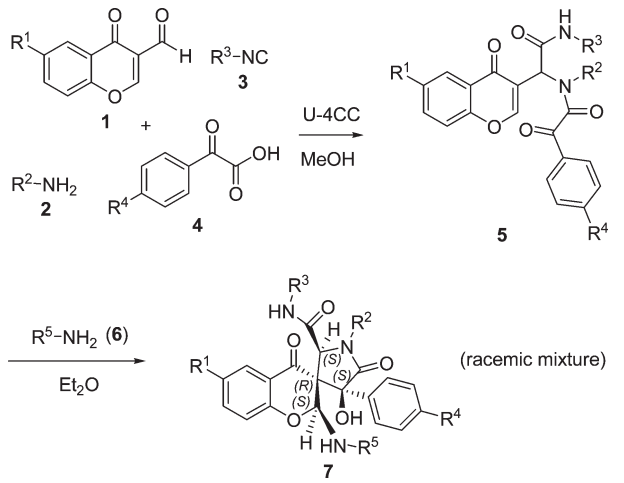
SCHEME 1. General Synthesis of Spiropyrrolidinochromanones



possible products. A more general synthesis of spiropyrrolidinobenzopyranes allowing a wide range of substituents would be a valuable strategy for the discovery of new biologically active compounds.

Multicomponent reactions (MCRs), and particularly those involving isocyanides (IMCRs), are highly convergent processes that have proven useful for the efficient preparation of complex molecules from simple starting materials.[17] One of the major interests of our laboratory is the combination of IMCRs with postcondensation transformations for the preparation of natural product-like heterocycles.[18] Furthermore, IMCRs have been used by us[19] and others[20] for the preparation of spiroheterocycles.

Here, we propose a versatile synthesis of spiropyrrolidinonechromanones based on an Ugi four-component condensation.[21] The advantage of this method is that a high degree of diversity can be attained by reacting, in a combinatorial way, five components in a one-pot, two-step, sequential process.

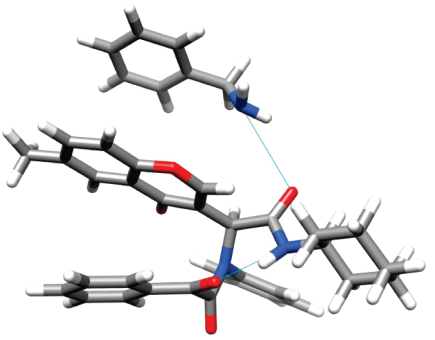


FIGURE 1. pm3-minimized model of (*S*)-**5a** being approached by benzylamine.

Our approach relies on the high reactivity of electron-deficient position 2 of chromones.[22] The addition of nucleophiles to this position generates a negative charge on carbon 3, which can be trapped with electrophiles. We intend to use an Ugi condensation to prepare chromones containing an electrophilic moiety able to trap the anionic intermediate generated by the addition of nucleophiles to chromone position 2.

In this way, it will be possible to obtain spiranic structures, in which each of the four components of the Ugi reaction and the nucleophile will provide an element of diversity. Theoretically, having a choice of just five different compounds of each of the five components, it would be possible to obtain more than 3000 different products.

To test our hypothesis, we performed the reaction between 6-methyl-3-formylchromone (**1**, $R^1 = CH_3$), aniline (**2**, $R^2 = C_6H_5$), cyclohexyl isocyanide (**3**, $R^3 = c\text{-}C_6H_{11}$), and phenylglyoxilic acid (**4**, $R^4 = H$) by simply combining the four components in methanol solution. Stirring the mixture at room temperature readily gave the expected Ugi four-component adduct **5a**, which was not isolated. Evaporation of the solvent and subsequent addition of diethyl ether and benzylamine (**6**, $R^5 = CH_2Ph$) led to the formation of spiropyrrolidinonechromanone **7a** (Scheme 1). As anticipated, conjugate addition of the amine to chromone carbon 2 generates an enolate anion which intramolecularly attacks the carbonyl on the glyoxylamide side chain, resulting in the formation of a new spiranic pyrrolidinone ring.

The reaction occurs with remarkably high diastereoselectivity: Three new stereogenic centers are formed in the cyclization process, and according to NMR data, only one diastereomer is obtained.

Semiempirical calculations on adduct **5a** reveal that particularly stable conformations exhibit a parallel arrangement of their chromone and glyoxylamide aromatic rings. This geometry minimizes unfavorable steric interactions and possibly favors π-stacking stabilization. On the other hand, in such conformations only one side of the chromone ring is available to the nucleophilic attack of benzylamine (Figure 1). We hypothesize that the carbonyl of the side chain amide group can form a hydrogen bond with the nucleophilic amine, "guiding" its approach to chromone carbon 2. Furthermore, the amide carbonyl can act as a general basic catalyst, enhancing the nucleophilic character of the amine and facilitating a successive transfer of the amine proton to the forming 4′ hydroxyl group.

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TABLE 1. Synthesis of Spiropyrrolidinonechromanones 7a−j

	R^1	R^2	R^3	R^4	R^5	yield[a,b] (%)
a	CH_3	C_6H_5	*c*-C_6H_{11}	H	$PhCH_2$	72
b	CH_3	C_6H_5	*c*-C_6H_{11}	H	3-Cl-$PhCH_2$	68
c	CH_3	C_6H_5	*c*-C_6H_{11}	H	*rac*-$C_5H_9OCH_2$[c]	70
d	CH_3	4-Cl-Ph	*c*-C_6H_{11}	H	(*S*)-$PhCH(CH_3)$	56
e	CH_3	4-Cl-Ph	*c*-C_6H_{11}	H	3,4-$(OCH_2O)PhCH_2$	57
f	H	3-Cl-Ph	*c*-C_6H_{11}	OCH_3	$PhCH_2$	63
g	H	3-Cl-Ph	*c*-C_6H_{11}	OCH_3	4-Cl-$PhCH_2$	58
h	H	$PhCH_2$	*c*-C_6H_{11}	H	3,4-$(OCH_2O)PhCH_2$	45
i	H	4-CH_3-Ph	$(CH_3)_3C$	H	3-Cl-$PhCH_2$	74
j	H	C_6H_5	2,6-$(CH_3)_2$-Ph	H	$PhCH_2$	68

[a]Experimental procedure and representative data are found in the Experimental Section. [b]Yields correspond to pure isolated products; procedures have not been optimized. [c]$C_5H_9OCH_2$: 2-tetrahydrofurfurylmethyl.

The structure shown in Figure 1 is the only stable conformation on which the amide carbonyl can assist the attack of benzylamine on the less hindered face of (*S*)-**5a**. Nucleophilic addition of benzylamine on the C-2 less hindered *Re* face of (*S*)-**5a** should produce sp^3-hybridized C-2 with *S* configuration. In a concerted mechanism, the *Re* face of the resulting transitional anion on C-3 must attack the neighboring glyoxylamide carbonyl, resulting in the formation of two stereocenters of respective configurations 3*R* and 2′*S*. According to this model, $\pi-\pi$ interaction of the benzylamine and chromone rings will further stabilize the transition state. Analogously, attack of benzylamine on enantiomeric Ugi adduct (*R*)-**5a** would obviously give the opposite spiranic enantiomer.

The structure and relative stereochemistry of compound **7a** was unequivocally determined by monocrystal X-ray diffraction analysis (see the Supporting Information). Hence, **7a** was assigned the structure (2*S*,2′*S*,3*R*,4′*S*)-2-(benzylamino)-*N*-cyclohexyl-4′-hydroxy-6-methyl-4,5′-dioxo-1′,4′-diphenylspiro-[chromane-3,3′-pyrrolidine]-2′-carboxamide (Figure 1). This structure is in accordance with the proposed mechanism.

In order to study the scope of the method, we applied the same procedure to different combinations of chromones (**1**), aromatic or aliphatic amines (**2**), aromatic or aliphatic isocyanides (**3**), glyoxilic acids (**4**), and primary amine nucleophiles (**6**). In all cases, we obtained the expected spiropyrrolidinochromanones **7a−j** in moderate yields (Table 1). Hence, the reaction was shown to be tolerant to a wide range of substituents on the different components. The products have been characterized by the usual spectroscopic techniques, and their IR, ^{1}H NMR, ^{13}C NMR, MS, and HRMS spectroscopic data are in agreement with the proposed structure. Table 1 summarizes the results of the tandem Ugi−nucleophilic addition−cyclization process.

Importantly, when nonchiral amines were used as nucleophiles, the product was always obtained as a single diastereomer (Table 1, entries a, b, e−j). We presume compounds **7b**, **e−j** all have the same stereochemistry as **7a**, as they must be formed by a similar reaction mechanism. In the case of using chiral amines (Table 1, entries c and d), its addition to both Ugi adduct enantiomers must result in the formation of two diastereomeric spiranes. Accordingly, both **7c** and **7d** were obtained as practically equimolar mixtures of two diastereomers as judged by its NMR spectra. We have also performed separate reactions with (*R*)-α-methylbenzylamine and with racemic (±)-α-methylbenzylamine (results not shown), obtaining an identical mixture of diastereomers as when using the *S* enantiomer (Table 1, entry d).

In summary, we have developed a practical method that allows obtaining, in a one-pot two-step sequential reaction, highly functionalized spiropyrrolidinonechromanones with a wide variety of substituents. Furthermore, we have shown that this reaction sequence can take place with high diastereoselectivity. The experimental simplicity of this method and the possibility to isolate the final products by filtration with a reasonable grade of purity makes it suitable for the combinatorial synthesis of libraries of potentially bioactive spiranes.

Experimental Section

General Procedure for the Synthesis of Spiropyrrolidinochromanones. 3-Formylchromone or 6-methyl-2-formylchromone (**1**) (2 mmol) was dissolved in MeOH (4 mL). The aniline (**2**) (2 mmol), isocyanide (**3**) (2 mmol), and phenylglyoxilic acid (**4**) (2 mmol) were successively added, and the resulting mixture was stirred for 24−48 h at rt, readily leading to the formation of the expected Ugi four-component adduct (**5**), which was not isolated. Evaporation of the solvent, resuspension in Et_2O (5 mL), and addition of amine **6** (4 mmol) led to the immediate formation of a precipitate. The reaction mixture was stirred at rt overnight, and the solid was filtered and washed with *i*-Pr_2O, yielding spiropyrrolidinochromanone (**7**) practically pure. For analytical purposes the product was further purified by recrystallization from EtOH.

Representative Data. 2-(Benzylamino)-*N*-cyclohexyl-4′-hydroxy-6-methyl-4,5′-dioxo-1′,4′-diphenylspiro[chromane-3,3′-pyrrolidine]-2′-carboxamide (7a): obtained as a white solid (72%); mp 172−172.5 °C; IR (cm^{-1}) 3440, 2933, 1682, 1636, 1493, 1284, 698; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (d, 1H, J = 7.3 Hz), 8.14 (s, 1H), 7.57 (d, 2H, J = 7.8 Hz), 7.50 (t, 2H, J = 7.7 Hz), 7.36 (t, 1H, J = 7.3 Hz), 7.21−7.07 (m, 6H), 7.04 (d, 1H, J = 8.4 Hz), 6.90 (m, 4H), 6.43 (d, 1H, J = 8.4 Hz), 5.70 (d, 1H, J = 12.0 Hz), 5.16 (s, 1H), 3.87−3.74 (m, 3H), 3.54−3.47 (m, 1H), 2.07 (s, 3H), 1.61−0.71 (m, 10H) ; ^{13}C NMR (100 MHz, DMSO-d_6) δ 190.4 (C), 171.4 (C), 168.9 (C), 153.9 (C), 139.0 (C), 136.9 (CH), 135.4 (C), 129.0 (C), 128.8 (CH), 128.2 (CH), 127.7 (CH), 127.7 (CH), 127.2 (CH), 126.9 (CH), 126.6 (CH), 126.0 (CH), 125.6 (CH), 125.0 (CH), 120.3 (C), 118.0 (CH), 88.8 (CH), 81.6 (C), 64.1 (CH), 61.3 (C), 49.4 (CH_2), 48.4 (CH), 31.3 (CH_2), 30.9 (CH_2), 24.9 (CH_2), 24.0 (CH_2), 23.7 (CH_2), 19.8 (CH_3); MS (FAB) m/z 630 ($M^+ + 1$, 56), 478 (6), 405 (100); HRMS (FAB) calcd for $C_{39}H_{40}N_3O_5$ 630.2968, found 630.2969.

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Supporting Information Available: Characterization data of the products, copies of ^{1}H and ^{13}C NMR spectra, X-ray crystallographic data of **7a**, and the CIF file for structure **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.