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Synthesis of 3-Aminomethyl-2-aryl-8-bromo-6-chlorochromones

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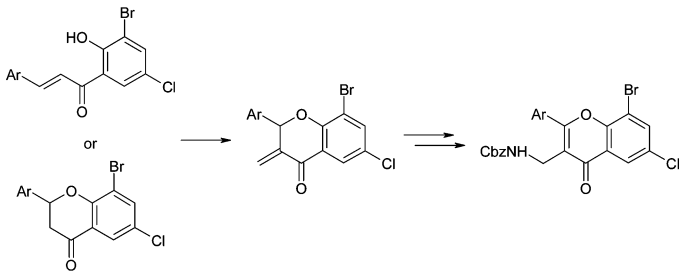
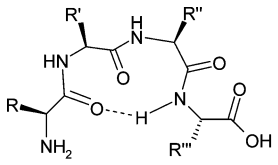
ABSTRACT



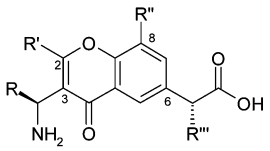
An efficient synthetic route to Cbz-protected 3-aminomethyl-2-aryl-8-bromo-6-chlorochromones has been developed. 3-Aryl-1-(3-bromo-5-chloro-2-hydroxyphenyl)-2-propen-1-one or 2-aryl-8-bromo-6-chlorochroman-4-one could be reacted under Mannich conditions yielding 2-aryl-8-bromo-6-chloro-3-methylenechroman-4-one, which was further converted to the target compound via an aza-Michael reaction followed by an SeO_2 oxidation. This procedure represents a new method to introduce a primary aminomethyl group at the 3-position of a 2-arylchromone scaffold. The Cbz-protected 3-aminomethyl-2-aryl-8-bromo-6-chlorochromones can, e.g., be used in the synthesis of chromone-based β-turn peptidomimetics.

Chromone (chromen-4-one) derivatives are interesting as structural scaffolds and have been assigned as privileged structures in drug development.[1] Chromones with different functionalized substituents have been proposed as mimetics of short peptides, as the conformation of a β-turn of a peptide (**1**) corresponds well with the 2,3,6,8-tetrasubstituted chromone **2**.[2] In addition, many flavonoids are based on the chromone structure. Several therapeutically interesting biological activities of the flavonoids have been reported.[3]

In a project aimed at the synthesis of chromone-based β-turn peptidomimetics, access to a suitably *N*-protected 3-aminomethyl-2-aryl-8-bromo-6-chlorochromone **3** was required.



1



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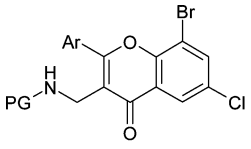

3

PG = protecting group

The use of a one-pot Mannich reaction and cyclization has been reported for the introduction of a tertiary aminomethyl group in the 3-position on 2-arylchromones;[4] how-

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(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.
(2) Dahlén, K.; Grøtli, M.; Luthman, K. In *Understanding Biology Using Peptides*; Blondelle, S., Ed.; American Peptide Society: San Diego, 2006; pp 677−678.
(3) Havsteen, B. H. *Pharmacol. Ther.* **2002**, *96*, 67−202.
(4) (a) Braa, M. F.; Morán, M.; Emling, F.; Schlick, E. *Drug Des. Discov.* **1994**, *11*, 329−334. (b) Rehse, U. *Arch. Pharm.* **1975**, *308*, 881−887.

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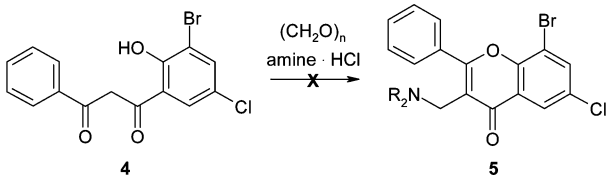
ever, much less is known on how to introduce primary or secondary amines. Our attempt to use this reaction to prepare **5** from **4** (Scheme 1) resulted only in trace amounts of

Scheme 1. Attempted One-Pot Reaction from **4** to **5**

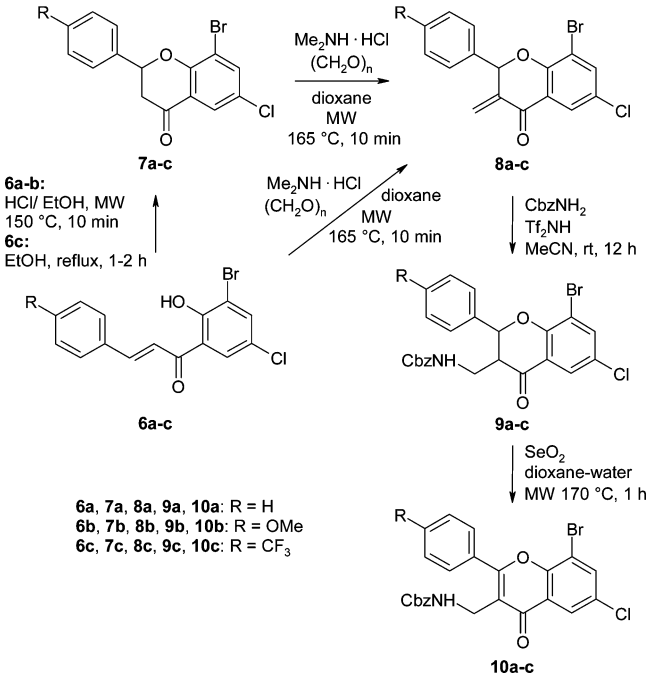


product **5** independent of amine (ammonia, primary and seconday amines), solvent, and temperature used.

Instead, we made attempts to synthesize **3** via a Mannich reaction on a 2-arylchroman-4-one derivative,[5] followed by oxidation to the corresponding chromone.

The Mannich reaction was investigated using a series of 2-aryl-8-bromo-6-chlorochroman-4-ones, **7a** (R = H), **7b** (R = OMe), and **7c** (R = CF_3) (Scheme 2). These starting

Scheme 2. Synthetic Route from **6** to **10**



materials were prepared via an acid-catalyzed ring closure of the corresponding chalcones **6a**−**c** in yields of 75, 55, and 98%, respectively.[6] The first attempt to perform the Mannich reaction on **7b** using dimethylamine hydrochloride, paraformaldehyde, and a catalytic amount of concentrated HCl in refluxing EtOH failed as only starting material was recovered.[7] A microwave-assisted procedure was adopted in which **7a**−**c** were reacted with dimethylamine hydrochloride and paraformaldehyde in dioxane in a microwave cavity at 165 °C for 10 min.[8] Interestingly, instead of obtaining the desired Mannich products,[9] all three starting materials gave the corresponding 3-methylene-chroman-4-ones **8a**−**c** as the only products without any unreacted starting material or impurities present.[10] 3-Methylenechroman-4-ones have been obtained before via the Mannich reaction, but only in low yields, as both the Mannich reaction and the following β-elimination have been reported to be low-yielding reactions (10−20% and 3−12%, respectively).[5a,b]

Accordingly, this observation inspired further testing of reaction conditions for the synthesis of **8**. Hence, compound **7c**[11] was reacted with paraformaldehyde in the presence of a catalytic amount of morpholine in refluxing acetic acid[12] or used in a piperidine-catalyzed aldol condensation with paraformaldehyde in dioxane.[13] Both reactions were run in a microwave cavity.[14] The reactions gave **8c** as the main product with several minor impurities. We did not continue to study these alternative reactions as our newly discovered method gave a cleaner product.

Compounds **8a**−**c** were found to slowly dimerize on standing in room temperature, and therefore, they were immediately used without prior purification.[15] Compounds **8a**−**c** were also useful for our synthetic approach, as an aza-Michael reaction would provide the desired Cbz-protected 3-aminomethylchroman-4-ones **9a**−**c**.

An aza-Michael reaction on the crude **8a**−**c** using $CbzNH_2$ in the presence of Tf_2NH in acetonitrile at room temperature was performed according to a recently reported procedure.[16] Compounds **9a**−**c** were obtained in overall yields of 69, 73, and 63%, respectively, calculated from **7a**−**c**. The isomer (cis/trans) ratio was 3:7 according to ^{1}H NMR spectroscopy. The major isomer was not assigned as the mixture of isomers was used in the next reaction step in which the asymmetry was destroyed.

Compounds **9a**−**c** were oxidized with SeO_2 in dioxane−water under microwave irradiation at 170 °C for 60 min to

(5) (a) Cingolani, G. M.; Gualtieri, F.; Pigini, M. *Il Farm.* **1971**, *26*, 718−25. (b) Ward, F. E.; Garling, D. L.; Buckler, R. T. *J. Med. Chem.* **1981**, *24*, 1073−1077. (c) Quaglia, W.; Pigini, M.; Gianella, M.; Melchiorre, C. *J. Med. Chem.* **1990**, *33*, 2948−2950.

(6) The chalcone **6c** cyclized upon heating in EtOH (recrystallization conditions) but the other chalcones **6a** and **6b** had to be heated in a microwave cavity in EtOH with a catalytic amount of HCl present at 150 °C for 20 min. Even then, the chalcones **6a** and **6b** did not give more than 75 and 55% conversion, respectively, the rest being mainly unreacted starting material in both cases.

(7) The other 2-aryl-8-bromo-6-chlorochroman-4-ones **7a** and **7c** were not tested using this procedure.

(8) Lehmann, F.; Pilotti, Å.; Luthman, K. *Mol. Divers.* **2003**, *7*, 145−152.

(9) Similar Mannich products have been reported to be unstable and undergo β-elimination (ref 5b).

(10) Purity verified by ^{1}H NMR spectroscopy.

(11) The other 2-aryl-8-bromo-6-chlorochroman-4-ones **7a** and **7b** were not tested using these procedures.

(12) Kim, M. Y.; Lim, G. J.; Lim, J. I.; Kim, D. S.; Kim, I. Y.; Yang, J. S. *Heterocycles* **1997**, *45*, 2041−2043.

(13) Gericke, R.; Harting, J.; Lues, I.; Schittenhelm, C. *J. Med. Chem.* **1991**, *34*, 3074−3085.

(14) The reactions were performed at 160 °C for 10 min.

(15) The structurally similar 6-cyano-2,2-dimethyl-3-methylenechroman-4-one was also reported to be unstable, forming the Diels−Alder dimer in solution (ref 13).

(16) Wabnitz, T. C.; Spencer, J. S. *Org, Lett.* **2003**, *5*, 2141−2144.

the corresponding chromones **10a**−**c** in 72−74% yield. A shorter reaction time gave a mixture of starting material and product.

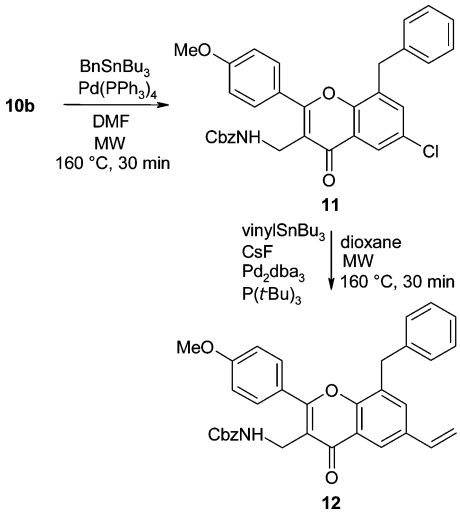
Since the ring closure of **6a**−**c** to **7a**−**c** and the following Mannich reaction are both acid-catalyzed reactions, the Mannich reaction conditions were tested using **6a**−**c** as starting material. We found that **6a**−**c** also gave **8a**−**c** as the only product. The Mannich reaction on **6b** gave an identical result as compared to the reaction on **7b**. However, **6a** and **6c** did not result in full conversion, and some unreacted starting material (20% and 30%, respectively) could be identified in the crude product mixture. Other reaction conditions were not studied for these two reactions. Nevertheless, the aza-Michael reaction was performed on all three crude products without removing unreacted starting material. Compounds **9a**−**c** were obtained in an overall yield of 62, 64, and 49%, respectively, calculated from **6a**−**c**. These yields were somewhat lower than when performing the Mannich reaction on **7a**−**c**. Compound **9c** had the largest drop in yield, from 63 to 49%, but it also showed the highest amount of unreacted starting material after the Mannich reaction.

Interestingly, when comparing the overall yields of **10a**−**c** calculated from **6a**−**c** for both reactions, it is obvious that **10a**,**b** should be prepared with the Mannich reaction directly on **6a**,**b**, but that **10c** should be prepared with a Mannich reaction on **7c**. In this way, all three compounds **10a**−**c** could be obtained with an overall yield above 45% from **6a**−**c**.

To demonstrate the applicability of the Cbz-protected 3-aminomethyl-2-aryl-8-bromo-6-chlorochromones **10** for the study of chromone-based peptidomimetics, we used **10b** in which a benzyl group was introduced in the 8-position and a vinyl group in the 6-position (Scheme 3). The two successive Stille cross-coupling reactions in 64 and 79% yields, respectively, were performed according to our previously reported procedures[17] and provided the Cbz-protected 3-aminomethyl-8-benzyl-2-(4-methoxyphenyl)-6-vinylchromone **12**, which can be used for the synthesis of a Gly-Tyr-Phe-Gly mimetic.

(17) (a) Dahlén, K.; Grøtli, M.; Luthman, K. *Synlett* **2006**, 897−900. (b) Dahlén, K.; Wallén, E. A. A.; Grøtli, M.; Luthman, K. *J. Org. Chem.* **2006**, *71*, 6863−6871. For the vinylation reaction, see also: Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 2411−2413.

Scheme 3. Pd-Mediated Reactions to Introduce Substitutents in Positions 8 and 6



In conclusion, a new method to introduce an aminomethyl group in the 3-position via a Mannich reaction can use either chalcones **6a**−**c** or chromones **7a**−**c** as starting materials. A short reaction sequence consisting of three or four steps, clean reactions and good overall yields make this an excellent method to introduce a primary aminomethyl group at the 3-position of both 2-arylchromone and chroman-4-one scaffolds. The Cbz-protected 3-aminomethyl-8-bromo-6-chloro-2-(4-methoxyphenyl)chromone **10b** was further demonstrated to be applicable to our study of peptidomimetics by the synthesis of **12**.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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