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Diastereoselective synthesis of 3,3-disubstituted 3-nitro-4-chromanone derivatives as potential antitumor agents†

Huiqing Chen,‡[a] Jia Xie,‡[b] Dong Xing,‡[a] Jinping Wang,[a] Jie Tang,[a] Zhengfang Yi,[b] Fei Xia,[a] Wen-Wei Qiu*[a] and Fan Yang*[a]

We report an efficient and highly diastereoselective protocol for the rapid construction of 3-nitro substituted 4-chromanones by an intramolecular Michael-type cyclization of α-nitro aryl ketones bearing unsaturated ester units. A catalytic amount of KO*t*Bu was found to be crucial for the high diastereoselective control of this transformation. With this protocol, a series of 3,3-disubstituted 3-nitro-4-chromanones were synthesized in good to excellent yields with high diastereoselectivities and showed moderate to good *in vitro* antitumor activities, representing promising antitumor hits for further drug discovery.

4-Chromanones constitute the framework of a large number of natural products and biologically active molecules, which have attracted significant attention due to their broad biological effects such as antibiotic,[1a] anti-inflammatory,[1b] anti-HIV,[1c] anti-mutagenesis[1d] and especially antitumor activities (Fig. 1, **A**, **B** and **C**).[1e–g] Among a number of pharmacological studies with 4-chromanone based compounds, Bauvois and coworkers reported that derivatives of 3-nitro-4-chromanones (Fig. 1, **D**) dose-dependently inhibited human AML U937 cells,[2a] and Arimondo and coworkers also discovered that a similar structural motif (Fig. 1, **E**) exhibited potent antiproliferative activity against L 1210 murine leukemia cells and human colon cancer HT29 cells.[2b] In these studies, it was found that the 3-nitro substituent on the 4-chromanone skeleton is crucial for their antitumor activities. Inspired by these interesting discoveries and related studies,[2] we perform the synthesis and pharmacological evaluation of new types of 3-nitro-substituted 4-chromanones. However, among a large number of methods for the construction of 4-chromanone skeletons,[3] such as intramolecular Stetter reaction,[4] intramolecular conjugated addition,[5] Mitsunobu reaction,[6] tandem cyclization[7] and many others,[8] methods for the synthesis of 3-nitro-substituted 4-chromanones have not been extensively investigated.[9–11] The known methods to introduce the 3-nitro substituent include the direction nitration of unsubstituted 4-chromanones, which generally requires harsh reaction conditions and shows a narrow substrate scope,[9] and intramolecular conjugated addition of phenol to nitro-substituted enones, in which the starting material is hard to prepare and the substrate scope is also narrow.[10] Towards these ends, the development of an efficient method for the preparation of new types of 3-nitro-substituted 4-chromanones is highly sought after and will greatly benefit the discovery of new 4-chromanone-based biologically active lead compounds.

By a simple retrosynthetic analysis, we envisioned that an intramolecular Michael-type cyclization of compound **B** from its α-nitro substituted ketone unit to the α,β-unsaturated ester group would allow an efficient way to construct 3-nitro substi-

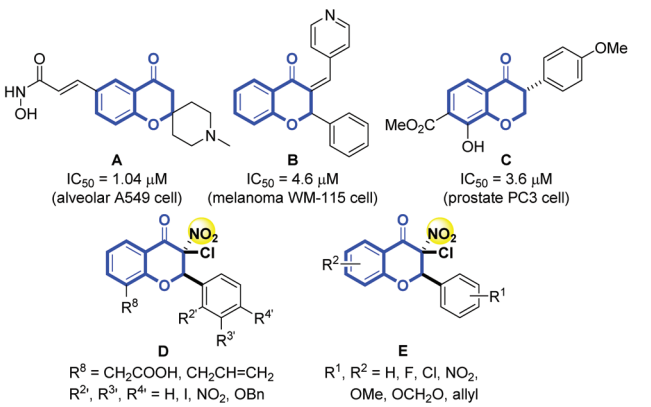

Fig. 1 Representative structures of antitumor 4-chromanones and 3-nitro-4-chromanones.

[a]*Shanghai Engineering Research Center of Molecular Therapeutics and New Drug Development, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai, 200062, China. E-mail: wwqiu@chem.ecnu.edu.cn, fyang@chem.ecnu.edu.cn*

[b]*Shanghai key Laboratory of Regulatory Biology, Institute of Biomedical Sciences and School of Life Sciences, East China Normal University, Shanghai, 200241, China*

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‡These authors contributed equally to this work.

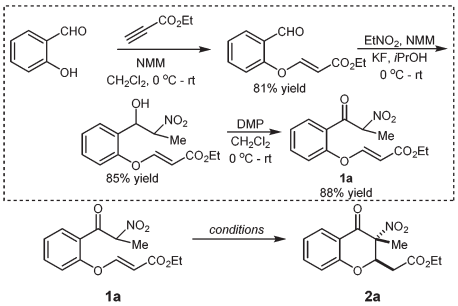
tuted 4-chromanones with a quaternary stereocenter (Scheme 1). Substrate **B** can be easily prepared from 2-hydroxyl-benzaldehyde, nitroalkane and alkynyl esters. Although this method seems easy to realize and quite straightforward, however, as the methylene group of the α-nitro ketone unit is very reactive, the desired Michael-type cyclization may proceed very fast, making the diastereoselectivity control a difficult task. Nonetheless, the rich chemistry on metal and/or organo-catalyzed transformations based on α-nitro carbonyl compounds would allow us to realize a good diastereoselective control of this transformation by choosing a suitable catalyst.[12]

Initially, the designed substrate **1a** was synthesized from α-hydroxy-benzaldehyde, ethyl propiolate and nitroethane *via* a three-step sequence with a good yield.[13] With this substrate in hand, different conditions for the designed Michael-type cyclization were tested. While **1a** did not undergo the desired cyclization in the absence of a base catalyst (Table 1, entry 1), the reaction occurred smoothly in the presence of organic base catalysts such as Et_3N, pyridine, DMAP and DBU, providing the desired cyclization product **2a** in high yields but with low diastereoselectivity (Table 1, entries 2–5). Different inorganic bases could catalyse this transformation with high efficiency and greatly improved diastereoselectivity, and the highest dr was observed when KO*t*Bu was used (Table 1, entries 6–12). By choosing KO*t*Bu as the catalyst, different solvents were tested (Table 1, entries 13–20). While nonpolar solvents such as toluene, 1,4-dioxane, and Et_2O gave similar dr to that of CH_2Cl_2 and protic solvents such as MeOH gave very poor dr, the use of THF as the solvent gave a further improved dr (Table 1, entry 16). The reaction was then conducted under different temperatures (Table 1, entries 21–24). It was found that lowering the temperature was beneficial for the diastereoselectivity, and the highest dr was observed when this reaction was conducted at −40 °C while the yield still remained excellent (Table 1, entry 24). Finally, while the efficiency of this reaction remained unaffected by the amount of the catalyst, the use of 10 mol% of KO*t*Bu was most optimal for the dr.[14]

With the optimized reaction conditions in hand, the substrate scope was then investigated (Table 2). For most α-nitro acetophenones, regardless of their substitution pattern and the electronic property on the aryl group, the cyclization proceeded smoothly to provide the corresponding 3-nitro-4-chromanones in good yields. However, decreased diastereoselectivities were generally observed for substrates bearing substituents on the aryl ring except for those yielding 6-MeO and 8-MeO substituted products (Table 2, entries 1–10). α-Nitro propiophenone derived from nitropropane also underwent the desired cyclization with excellent yield and good dr (Table 2, entry 11). Substrates bearing different ester groups including *n*-butyl, phenyl, cyclohexanyl and adamantyl esters were all suitable substrates, yielding the corresponding 4-chromanones in high to excellent yields with moderate to high dr (Table 2, entries 12–16). Surprisingly, the relatively bulky adamantyl ester group gave the corresponding cyclization product with a much lower dr (Table 2, entry 16). Finally, the relative configuration of the product was determined as (2*R**,3*R**) by the X-ray crystallographic analysis of **2f** (Fig. 2).[15]

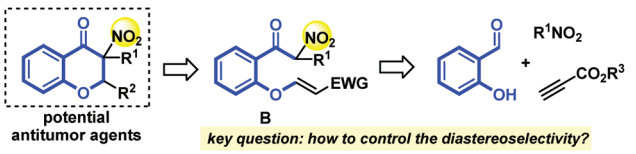
A possible pathway for this transformation was proposed as shown in Scheme 2. First, substrate **1a** was deprotonated into its enolate form **A**, which underwent an intramolecular Michael-type addition to generate a cyclized intermediate fol-

Table 1 Optimization of conditions[a]



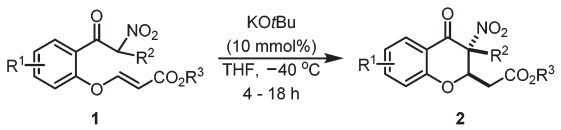
Entry	Catalyst (10 mol%)	Solvent	Temperature (°C)	Yield of **2a**[b] (%)	dr[c]
1	—	CH_2Cl_2	0	<5	—
2	Et_3N	CH_2Cl_2	0	89	1 : 1
3	Pyridine	CH_2Cl_2	0	80	2.2 : 1
4	DMAP	CH_2Cl_2	0	89	1.2 : 1
5	DBU	CH_2Cl_2	0	91	2.1 : 1
6	Cs_2CO_3	CH_2Cl_2	0	92	8.3 : 1
7	K_2CO_3	CH_2Cl_2	0	92	8.7 : 1
8	KOH	CH_2Cl_2	0	93	8.6 : 1
9	KO*t*Bu	CH_2Cl_2	0	94	9.0 : 1
10	NaO*t*Bu	CH_2Cl_2	0	94	7.4 : 1
11	NaOEt	CH_2Cl_2	0	93	7.7 : 1
12	NaOMe	CH_2Cl_2	0	93	6 : 1
13	KO*t*Bu	Toluene	0	70	9.4 : 1
14	KO*t*Bu	1,4-Dioxane	0	>95	9.7 : 1
15	KO*t*Bu	Et_2O	0	84	10.5 : 1
16	KO*t*Bu	THF	0	>95	12.3 : 1
17	KO*t*Bu	EtOAc	0	83	11.3 : 1
18	KO*t*Bu	Acetone	0	75	9.4 : 1
19	KO*t*Bu	DMSO	0	75	10.8 : 1
20	KO*t*Bu	MeOH	0	72	1.9 : 1
21	KO*t*Bu	THF	−10	91	14 : 1
22	KO*t*Bu	THF	−20	91	14.5 : 1
23	KO*t*Bu	THF	−30	93	16.2 : 1
24	KO*t*Bu	THF	−40	>95	20 : 1

[a] Reaction conditions: **1a** (1 mmol), catalyst (10 mol%), solvent (5 mL). NMM: *N*-methylmorpholine; DMP: Dess–Martin periodinane; DMAP: 4-dimethylaminopyridine; DBU: 1,8-diazabicyclo[5,4,0]undec-7-ene. [b] Isolated yield after column chromatography; "<5%" means that the corresponding product was not observed by ^{1}H NMR analysis of the crude mixture. [c] Determined by ^{1}H NMR of the crude mixture.



Scheme 1 Design of an intramolecular Michael addition strategy for the construction of 3,3-disubstituted-3-nitro-4-chromanone derivatives.

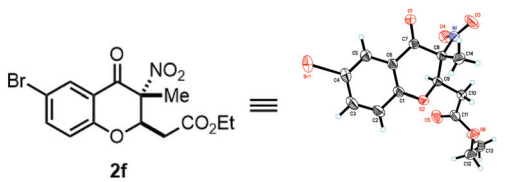
Table 2 Substrate scope[a]



1 2

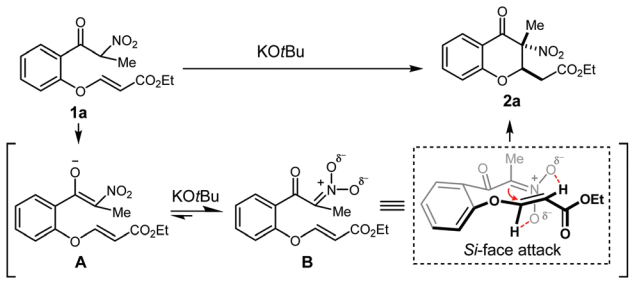
Entry	2	R^1	R^2	R^3	Yield[b] (%)	dr[c]
1	**2a**	H	Me	Et	95	20 : 1
2	**2b**	6-Me	Me	Et	92	13 : 1
3	**2c**	6-CF_3	Me	Et	92	10 : 1
4	**2d**	6-F	Me	Et	92	10 : 1
5	**2e**	6-Cl	Me	Et	92	11 : 1
6	**2f**	6-Br	Me	Et	93	11 : 1
7	**2g**	5-MeO	Me	Et	94	13 : 1
8	**2h**	6-MeO	Me	Et	93	17 : 1
9	**2i**	7-MeO	Me	Et	95	13 : 1
10	**2j**	8-MeO	Me	Et	94	>20 : 1
11	**2k**	H	Et	Et	92	14 : 1
12	**2l**	H	Me	Me	92	20 : 1
13	**2m**	H	Me	*n*-Bu	92	12 : 1
14	**2n**	H	Me	Ph	92	18 : 1
15	**2o**	H	Me	Cy	86	16 : 1
16	**2p**	H	Me	Ad	77	9 : 1

[a] Reaction conditions: **1** (1 mmol), KO*t*Bu (10 mol%), THF (5 mL). [b] Isolated yield after column chromatography. [c] Determined by ^{1}H NMR of the crude mixture.



2f

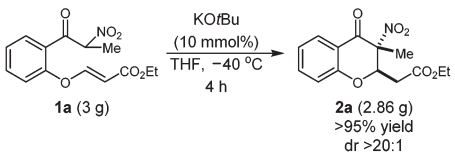
Fig. 2 X-ray crystal structure of compound **2f**. The thermal ellipsoids are drawn at 30% probability.



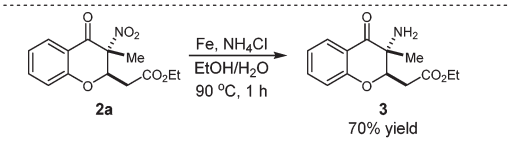
Scheme 2 Proposed mechanism and explanation of the stereochemistry.

lowed by proton transformation to give 4-chromanone **2a**. While the exact reason for the high dr of this reaction is unclear, it was possible that a catalytic amount of KO*t*Bu under lower temperature may accelerate the kinetically favored formation of enolate **B**,[16] and the favored conformation of the product may come from a *Si*-face attack owing to a π–π interaction between the nitro and ester carbonyl group and hydrogen bonding between the nitro oxygens and the olefinic protons. In the absence of KO*t*Bu or with weaker bases, the formation of enolate **B** was incomplete, and both *Si* and *Re*-face attacks from enolate **A** might happen and lead to low dr of the cyclized product. The poor dr observed for the substrate bearing an adamantyl ester group might be caused by the much bulkier adamantyl that led to a weaker π–π interaction between the nitro and ester group.

To demonstrate the synthetic potential of this transformation, we explored a gram-scale reaction. This transformation could be easily scaled up, making it very attractive and convenient for further structure modifications. As shown in eqn (1), the use of 3 g of **1a** produced 2.86 g of **2a** in 95% yield while the diastereoselectivity remained excellent. On the other hand, the 3-nitro-4-chromanone product **2a** can be easily reduced to 3-amino-4-chromanone **3** in a good yield by using Fe/NH_4Cl as the reductants (eqn (2)).[17]



(1)



(2)

The newly synthesized 3-nitro-4-chromanones **2a–p** and **3** were evaluated against the growth of various tumor cell lines, and it was found that they are more sensitive on prostate cancer DU145 and PC3 cells using the SRB (sulforhodamine B) assay (Table 3). Cisplatin was used as the positive control. The results showed that only a part of these compounds possessed moderate to potent antiproliferative activity. The adamantyl ester modified **2p** showed the most potent antiproliferative activity with IC_{50} values of 2.54 and 10.60 μM on DU145 and PC3 cell lines, respectively, which was slightly more potent than cisplatin. One of the major hindrances for the druggabil-

Table 3 IC_{50} values of 3-nitro-4-chromanones against the growth of prostate cancer cell lines

		IC_{50}[a] (μM)		
Entry	Compound no.	DU145	PC3	HAF
1	**X**[b]	>50	>50	>200
2	**2b**	45.50	>50	>200
3	**2c**	22.89	22.14	>200
5	**2e**	39.26	>50	>200
13	**2m**	21.08	>50	>200
15	**2o**	20.91	32.93	>200
16	**2p**	2.54	10.60	160.90
18	Cisplatin	3.13	11.04	41.13

From the SRB assay after 96 h of treatment. [a] IC_{50} data are an average of at least 3 independent experiments, variation ±10%. [b] X = compounds **2a**, **2d**, **2f–2l**, **2n** and **3**.

ity of candidate compounds is their toxicity to normal cells. Thus, it is important to test the cytotoxicity on normal cells in antitumor drug discovery. Compounds **2a–p** and **3** were chosen for the selectivity test on a normal human fibroblast (HAF) cell line using the SRB assay. The selectivity indexes (SI) were calculated by dividing the IC_{50} values in HAF by the IC_{50} values in the prostate cancer cell lines. The results disclosed that these 3-nitro-4-chromanones were less toxic on human fibroblasts in comparison with the tumor cells. The most active compound **2p** (SI = 15.2 and 63.3) showed 15.2 and 63.3 times higher selectivity towards cancer cells than towards human fibroblasts, which were more than 4-fold better than those of cisplatin (SI = 3.7 and 13.1).

In summary, an efficient and highly diastereoselective KO*t*Bu-catalyzed intramolecular Michael-type cyclization of α-nitro aryl ketones bearing unsaturated ester units was reported. With this method, a series of 3,3-disubstituted 3-nitro 4-chromanones bearing a tertiary stereocenter were synthesized in high to excellent yields with good to high diastereoselectivities. KO*t*Bu plays a crucial role both in accelerating the reaction rate and in improving the diastereoselectivities of this transformation. Some of the newly synthesized 3-nitro-4-chromanones displayed promising *in vitro* antiproliferative activity and good selectivity indexes (SI) between normal cells and cancer cells, and could be used as promising antitumor hits for further development. Further studies on structure modification and biological evaluation are currently ongoing.

Conflicts of interest

The authors declare no conflicts of interest.

Acknowledgements

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17 C. Lu, B. Kirsch, C. K. Maurer, J. C. de Jong, A. Braunshausen, A. Steinbach and R. W. Hartmann, *Eur. J. Med. Chem.*, 2014, **79**, 173.

