RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis of 4-Quinolones, Benzopyran Derivatives and other Fused Systems Based on the Domino ANRORC Reactions of (*Ortho*-fluoro)-3-benzoylchromones.

Viktor O. Iaroshenko,*[a,b] Satenik Mkrtchyan,[a] Ashot Gevorgyan,[a] Tatevik Grigoryan,[a] Alexander Villinger[a] and Peter Langer*[a,c]

[a] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany;

[b] National Taras Shevchenko University, 62 Volodymyrska st., Kyiv-33, 01033, Ukraine;

[c] Leibniz-Institut für Katalyse e. v. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany.

eceived (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Herein we reported a transition metal free strategy for the synthesis of 4-quinolones, benzopyran derivatives and other fused systems by the domino reaction of 3-benzoyl-chromones, containing a leaving group in the position-2 of the benzoyl moiety, with aliphatic amines, anilines and different binucleophiles. The developed strategy is suitable for a broad range of substrates, namely according to applied nucleophile the reaction provides different final products with excellent chemoselectivity. The mechanistic studies resulted in detection and isolation of several intermediates.

Introduction

A major challenge in organic synthesis today is to devise reactions that can form several C-C and/or C-heteroatom bonds in one operation leading to the construction of target structures with proper chemo-, regio- and stereoselectivity. In this context domino (also known as tandem or cascade) reactions have proven to be a powerful shortcut for the assembly of complex ring systems minimizing the waste sub-products and synthetic efforts.[1] During last three decades domino strategies were successfully applied in the synthesis of various practically valuable cyclic compounds including heterocycles, pharmaceuticals and natural products.[1,2]

Owing to their special electronic properties[3] the chemistry of heterocyclic systems like pyrones, chromones and their 3-acyl derivatives, have experienced a renaissance in recent years, namely they are often involved in domino transformations since the push-pull fragment in pyrone remains labile towards the external and internal nucleophiles (Figure 1).[4] On this basis for over a decade our group[5] and others[6-8] had developed several facile protocols utilizing chromones as suitable 1,3-CCC-dielectrophile building blocks for the synthesis of diverse complex ring systems including natural product and drug related molecular frameworks (Figure 1).

Considering the tendency of chromone framework to undergo an ANRORC (Addition of the Nucleophile, Ring Opening, and Ring Closure) transformation with various nucleophiles leading to the synthesis of numerous valuable systems[4-8] along with recent successes of our group with 4-quinolones and other systems,[9] we launched a program focusing on domino reactions of a new chromone substrate. The (*ortho*-fluoro)-3-benzoylchromones contain multiple electrophilic sites and a good leaving group (fluorine) which in fact makes them a common substrate for the synthesis of diverse and distinct molecular scaffolds under the influence of different nucleophiles (Figure 1).

Herein we report an efficient and concise TM-free (transition metal free) cascade reaction sequences for the synthesis of diverse molecular frameworks from (*ortho*-fluoro)-3-benzoylchromones. Particularly, the current approach enables the synthesis of synthetically challenging 4-quinolones and other valuable systems *via* exploiting the diverse functional sites on the multifunctionalized chromone. Our strategy drastically departs from traditional approaches for the synthesis of 4-quinolones and other valuable ring-systems presented in the work.[10] Moreover, we could demonstrate the advantage of using fluorine as a leaving group, in TM-free cascade reactions, over other halides which usually demand Pd-catalyzed protocols. These findings will significantly expand the value of chromones in the synthesis of heterocycles since 4-quinolone derivatives represent one of the important classes of antibiotics.[11]

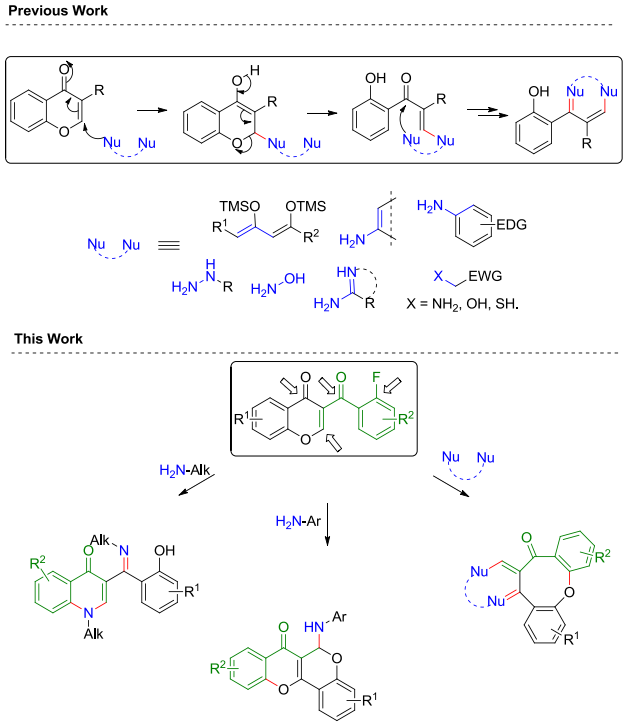
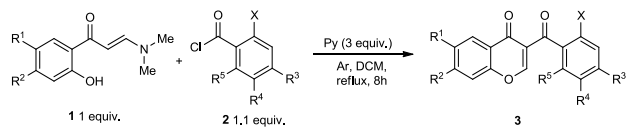


Figure 1. Domino transformations of chromones.

Results and Discussion

Accordingly, starting 3-benzoyl-4*H*-chromen-4-ones **3a-k** were easily prepared by reaction of appropriate enaminone **1** with corresponding benzoyl chloride **2**, and obtained in good yields (60-88%) (Table 1).

Table 1. Synthesis of starting chromones.



compound	X / R^1 / R^2	R^3 / R^4 / R^5	yield (%)[a]
3a	Br / H / H	H / H / H	73
3b	Cl / H / H	H / H / H	69
3c	F / H / H	H / H / H	78
3d	F / Me / H	H / H / H	80
3e	F / H / OMe	H / H / H	88
3f	F / Cl / H	H / H / H	71
3g	F / Cl / Me	H / H / H	68
3h	F / H / H	F / H / H	60
3i	F / H / H	H / F / H	80
3j	F / Br / H	H / F / H	67
3k	F / H / H	H / H / F	65

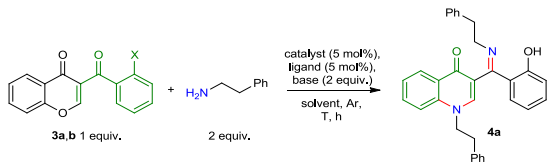
[a] Isolated yields.

With the synthetic concept in hand, accordingly we focused our attention on the chromones **3a**,**b** which are promising substrates for the tandem Pd-catalyzed Buchwald-Hartwig/Michael amination reaction towards the synthesis of 4-quinolones. As model coupling partner the phenethylamine was taken (Table 2).

The catalyst system was explored based on the Pd-containing compounds with loading of the typical ligands for Buchwald-Hartwig amination[12] namely DPEPhos, DavePhos, BINAP, Xantphos and P(^{t}Bu)$_3$. Besides, ligand free conditions along with the copper(I) catalysts[13] were examined. Some representative examples are depicted in the Table 2. However, our attempts were not satisfying. Indeed, we were able to prepare the desired heterocyclic system; nevertheless, the overall yields never exceeded 18% (Table 2, entry 3). The combination of Pd(PPh$_3$)$_4$ with BINAP using K_2CO_3 as a base in DMF at 120 ^{o}C turned to be the best conditions for this transformation (Table 2, entry 3).

After these unexpected failures, further we focused our attention on the investigation of TM-free reactions. Fortunately, we found that in the absence of catalyst the base in DMA at 160 ^{o}C can initiate the formation of corresponding 4-quinolone **4a** from chromone **3b** (X = Cl) in 17% yield (Table 2 entry 11). These circumstances prompted us to test some other good leaving groups which are often used in nucleophilic aromatic substitution. For this purpose we chose the fluorine[14,9a] installed in the *ortho*-position of benzoyl fragment of corresponding chromones **3c-k** (Table 1).

Table 2. Optimization of reaction conditions towards chromones **3a**,**b**.



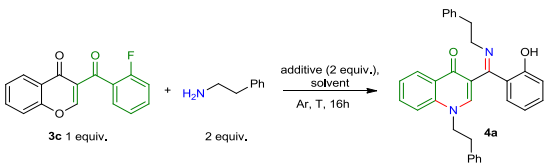
entry	X	catalyst / ligand	solvent / base	T / h	yield (%)[a]
1	Br	Pd(dba)$_2$ / DPEPhos	DMF / Cs_2CO_3	120°C / 16h	10
2	Br	Pd(PPh$_3$)$_4$ / BINAP	DMF / Cs_2CO_3	120°C / 16h	12
3	**Br**	**Pd(PPh$_3$)$_4$ / BINAP**	**DMF / K_2CO_3**	**120°C / 16h**	**18**
4	Br	Pd(PPh$_3$)$_4$ / BINAP	DMF / NaOEt	120^{o}C / 16h	8
5	Br	Pd(PPh$_3$)$_4$ / BINAP	Toluene / NaOEt	reflux / 36h	6
6	Br	Pd(PPh$_3$)$_4$ / BINAP	Dioxane / NaOEt	reflux / 16h	9
7	Br	Pd(PPh$_3$)$_4$ / BINAP	DMF / TEA	120°C / 16h	-
8	Br	-	DMF / K_2CO_3	160°C / 72h	-
9	Br	CuI / DMEDA	DMF / K_2CO_3.	120°C / 10h	-
10	Cl	Pd(PPh$_3$)$_4$ / BINAP	DMF / K_2CO_3	120°C / 16h	-
11	**Cl**	**-**	**DMA / K_2CO_3**	**160°C / 72h**	**17**

[a] Isolated yields.

We continued our studies by exploring the reaction between chromone **3c** and phenethylamine to optimize the reaction conditions (Table 3). When conducting first experiments with these compounds to test their ability to undergo cyclization cascade initiated by TMSCl,[4a,5,6] as a powerful water scavenger,[15] unfortunately we found that the presence of TMSCl suppresses the current transformation (entry 1). In spite of some conversion of starting materials no product was observed.

Subsequently, we examined several bases in polar solvents, such as DMF, NMP, or DMA, and were pleased to find that triethylamine initiates the formation of 4-quinolone derivative **4a** in DMF at 100 °C in 57% yield with complete chemoselectivity (Table 3, entry 2). Table 3 compiles the effects of base, solvent, and temperature on the outcome of the domino process. In early stages of the screening triethylamine appeared to be the optimal base. However the combination of DMF as the solvent and K_2CO_3 as the base was found to have the highest potential (Table 3, entry 5, 8, 9). Generally variation of the base and temperature was the key to further increase the yield. While the triethylamine / DMF / 100 °C system (entry 2) led to lower yields of the product, K_2CO_3 / DMF / 120 °C system (entry 5) appears to correspond to the optimal reactivity. In chosen system of reactants we could not prevent the Schiff base formation with the second molecule of amine, even though the amount of amine was reduced to 1 equivalent. The reaction proceeds stereoselectively leading to the formation of Z-imines. The stereochemistry of the reaction was proved by X-ray analysis (see SI). Besides, for all imines a hydrogen bond between N and OH groups was clearly seen in ^{1}H NMR spectra of 4-quinolones which is not possible for E-stereoisomers. The hydrogen bonding may be the driving force for stereoselective formation of Z-isomers.

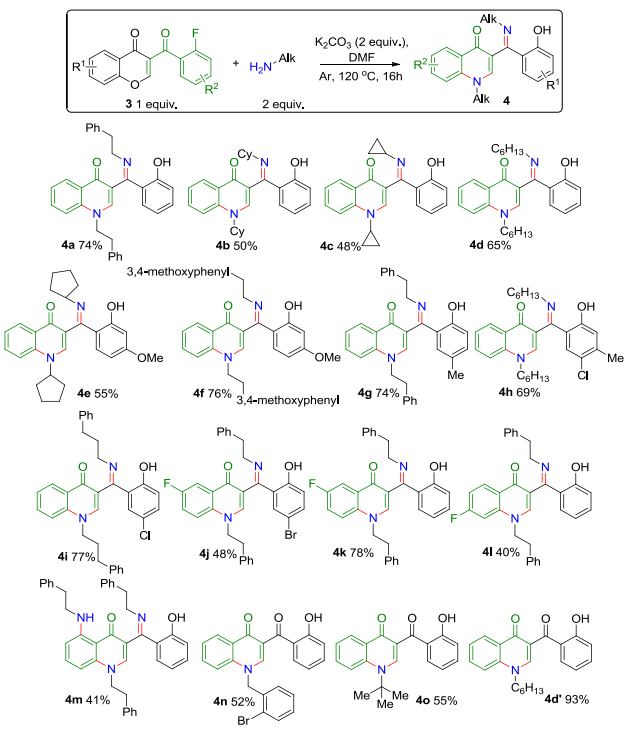
Table 3. Optimization of reaction conditions towards chromone **3c**.



entry	additive / solvent	T	yield (%)[a]
1	TMSCl / DMF	100°C	-
2	TEA / DMF	100°C	57
3	TEA / Toluene	100°C	18
4	Py / DMF	120°C	60
5	**K_2CO_3 / DMF**	**120°C**	**75**
6	Li_2CO_3 / DMF	120°C	73
7	K_3PO_4 / DMF	120°C	64
8	K_2CO_3 / DMA	120°C	72
9	K_2CO_3 / NMP	120°C	68

[a] Isolated yields.

Having optimized the reaction conditions, we prepared a variety of 4-quinolones **4a-o** with different substituents and explored the scope and generality of this domino reaction sequence (Scheme 1). All reactions proceeded well and provided the desired products **4** from moderate to good yields, with complete conversion of chromone and excellent chemoselectivity. In all cases the electron-withdrawing and electron-donating substituents on the chromone moiety were tolerated. Importantly, halogen functional groups, F, Cl, and Br, were compatible with the optimized reaction conditions, thereby enabling subsequent modifications at the halogenated positions. Namely, only in case of chromone **3k** with second fluorine in the *ortho*-position of carbonyl group, expectedly substitution of second fluorine with amine accrued leading to single product **4m** in 41% yield.[9a] These results demonstrate the high versatility, mildness, and high functional-group tolerance of this novel domino reaction. Furthermore, when bulky *tert*-butylamine and (2-bromophenyl)methanamine were used, the corresponding 4-quinolones **4n**,**o** were formed with excellent chemoselectivity. In addition compound **4d** can be easily transformed to corresponding 4-quinolone **4d'** *via* a simple reflux in acetic acid for 3 hours (Scheme 1). Since 4-quinolones are ubiquitous in bioactive substances,[11] polysubstituted 4-quinolones are important target structures, hence the novel synthetic route toward 4-quinolones having a specific substitution pattern is of special value. In this context the domino reaction sequence was also carried out on a gram scale. That is we could prepare the 4-quinolone **4a** in 10 gram scale with 74% yield. Thus, this reaction might be suitable for scale-up and large-scale chemical production.

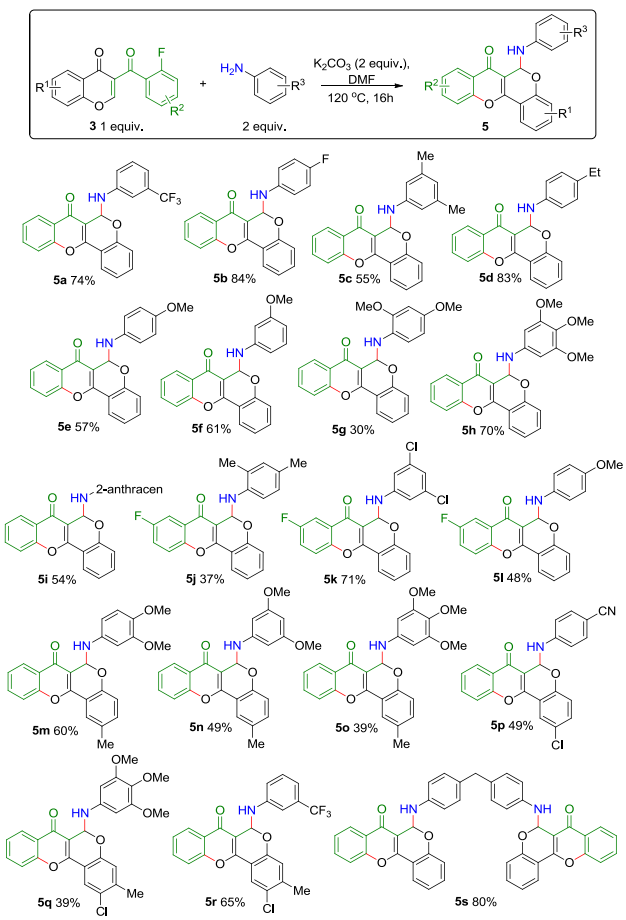


Scheme 1. The scope and generality of the reaction towards aliphatic amines.

To further expand the scope of the reaction, we treated the model chromone **3c** with anilines under the standard conditions. Surprisingly, instead of appropriate 4-quinolone corresponding benzopyran derivatives[16] with a stereogenic center **5** were formed in moderate yields (Scheme 2).

Notably, for anilines we found that the presence of moisture was essential, since the use of either argon atmosphere or rigorously dried reaction components resulted in only trace amounts of product **5**. This suggests that the presence of water affects the reaction in terms of yields. In general the reactions were conducted under open-flask conditions without addition of water. The reaction outcome was predictable in all cases, and products **5a-s** were typically obtained in good yields. The scalability of the reaction was demonstrated on the instance of chromone **3c** and 3-(trifluoromethyl)aniline. When run on a 5 mmol scale, the desired product **5a** was obtained in 74% yield. Additionally, the procedure can be effectively applied for bianilines (Scheme 2, **5s**).

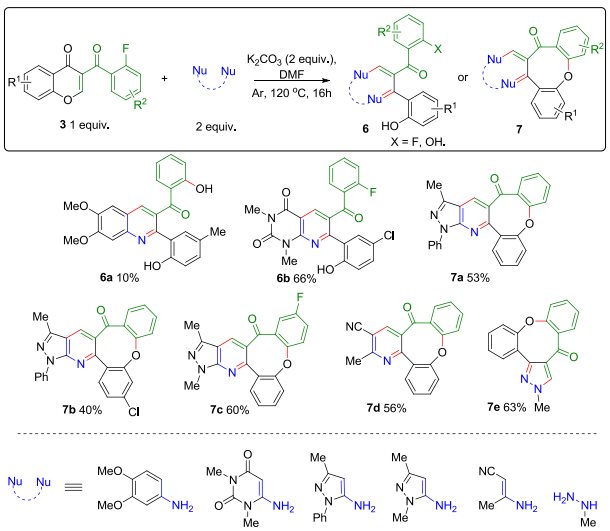
Interestingly, the use of anilines with electron-withdrawing functionalities afforded corresponding products **5** in higher yields and chemoselectivity (Scheme 2). However, the usage of anilines with electron-donating functionalities turned to be less effective. Thus, the electronic nature of the aniline significantly influences on the reaction outcome. In this context from the reaction of chromone **3d** and 3,4-dimethoxyaniline along with corresponding benzopyran derivative **5m** (60%) an interesting by-product namely the quinoline derivative **6a** was isolated in 10% yield. This indicates the presence of an additional and competing reaction pathway in which the aniline may behave as an enamine-like binucleophile (Figure 1, Scheme 3).



Scheme 2. The scope and generality of the reaction towards anilines.

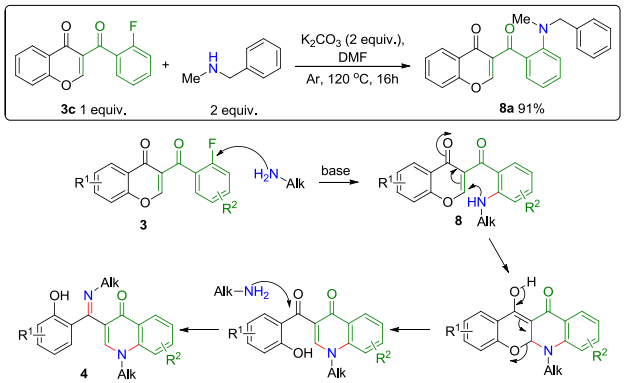
Intrigued by this finding we set out to investigate the transformation in detail. When other binucleophiles, like electron-excessive aminoheterocycles, enamines and hydrazines were used instead of electron-rich anilines, the reaction went smoothly *via* the new pathway to give corresponding products **6b**, **7a-e** in synthetically useful yields and chemoselectivity (Scheme 3). The preference of this pathway over the reaction pathway of anilines under the present reaction conditions is possibly due to the enhanced binucleophilic character of chosen nucleophiles which is the driving force that facilitates the chemoselectivity of the reaction.[5,6] As a result, polyfunctional complex molecules **7a-e** with three new bonds and a new ring system were rapidly generated through this one-pot domino reaction.

Many reaction pathways are possible in this complex reaction system. To explore the mechanism of cascade reaction between aliphatic amines and chromones the reaction of chromone **3c** with a secondary amine was performed using standard reaction conditions. Interestingly, corresponding amino-substituted chromone **8a** was isolated in almost quantitative yield (Scheme 4). Proposed reaction mechanism based on the results discussed above and previous reports (Figure 1)[5-8] is shown in Scheme 4.



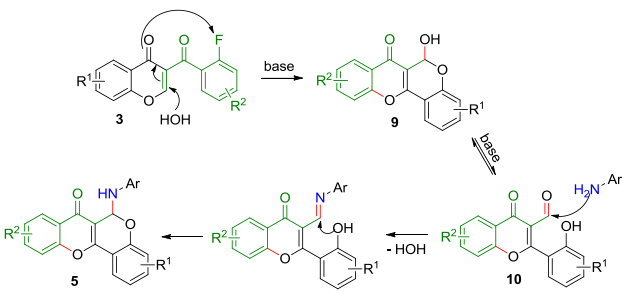
Scheme 3. The scope and generality of the reaction towards binucleophiles.

We suppose that the domino sequence is initiated by the aromatic nucleophilic substitution of fluorine atom. This is followed by the intramolecular attack of amino group to the position 2 of chromone moiety. Finally the ANRORC transformation of the pyrone ring delivers desired 4-quinolones. In most of the cases this is not the final step, the reaction runs further with second molecule of amine leading to the formation of corresponding Schiff bases **4**.



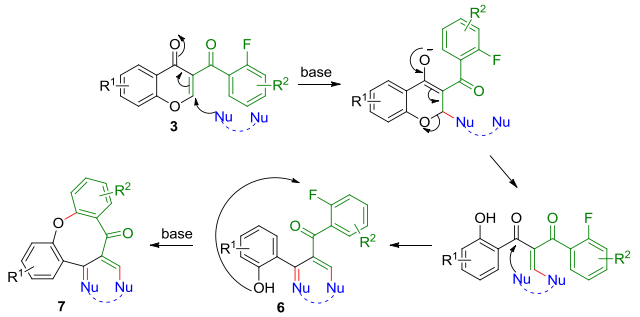
Scheme 4. Possible mechanisms of the reaction between chromones and aliphatic amines.

As it was mentioned, the trace amount of water had an effect on the outcome of the reaction between chromones and anilines, suggesting that the reaction starts with nucleophilic attack of water onto the position 2 of pyrone fragment, which gives rise to the intermediate **9** (Scheme 5). We could verify this, *via* isolation and characterisation of intermediate **9a** ($R^1 = R^2 = H$). Further the hemiacetal **9** can rearrange to free aldehyde form **10**,[17] which can be attacked by aniline, giving rise to corresponding Schiff base. Finally, the imine in basic conditions can be transformed to appropriate hemiaminal **5**. Noteworthy, the treatment of intermediate **9a** with 3-(trifluoromethyl)aniline in standard reaction conditions afforded the desired product **5a**. Additionally, the derivative of **9a**, namely 6-hydroxy-6-methylchromeno[4,3-*b*]chromen-7-on[18] was previously reported along with the existence of the ring-chain tautomerism between the hemiacetal **9** and the corresponding phenolic ketone **10**. This tautomeric equilibrium was proved by the U.V. absorption.[18]



Scheme 5. Possible mechanisms of the reaction between chromones and anilines.

A plausible mechanism of reaction between chromones and different binucleophiles is presented in Scheme 6. We assume that the domino sequence initiates the attack of nucleophile to the position 2 of chromone moiety. This is followed by the pyrone ring opening and further intramolecular nucleophilic attack of nucleophile onto the carbonyl group leading to intermediate **6**. Finally, in most of the cases this is not the final step, the reaction runs further by the intramolecular aromatic nucleophilic substitution of fluorine atom delivering corresponding fused systems **7**.



Scheme 6. Possible mechanisms of the reaction between chromones and binucleophiles.

All products listed were fully characterized by 1D NMR and 2D NMR methods, and confirmed by X-ray crystallography (**3e**, **4a**, **4b**, **4j**, **4l**, **7a**, **7c**, **7e**, **9a**, see SI).[19]

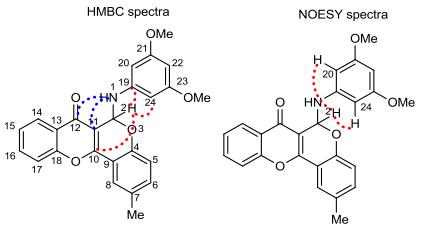


Figure 2. 2D NMR study of compound **5n**.

The structure of compounds **5a-s** was proven by 2D NMR spectroscopy (Figure 2). Particularly based on HSQC spectra the proton at 7.02-7.10 ppm (DMSO-d_6) turned to be N*H* group instead of CH. Accordingly, the C*H* proton next to the NH group gives a doublet at 6.6-6.9 ppm (DMSO-d_6). Furthermore, in HMBC spectra of compound **5n** the correlation between N*H* and carbons C-11 and C-12, as well as the correlation between C*H* and carbons C-10, C-19, C-24 were seen (Figure 2). Additionally, in NOESY spectra the correlation between the C*H* and the *ortho*-CH groups of aniline moiety was well observed. The peak of stereogenic center *C*H in ^{13}C NMR spectra was detected at 76.4-77.8 ppm (DMSO-d_6).

Conclusions

In summary, three unprecedented metal-free domino reactions starting from 3-benzoyl-4*H*-chromen-4-ones have been disclosed. This method provides a valuable one-pot shortcut for the synthesis of 4-quinolones, benzopyran derivatives and other fused systems and exhibits a broad substrate scope with excellent functional group tolerance. This is a striking example of how to determine the domino reaction pathway by simply switching between appropriate nucleophiles and reaction parameters. Detailed studies on the mechanism and the extension of these cascade reactions are currently underway in our laboratory.

Experimental Section

General Information

The dry solvents were purchased. Other solvents were purified by distillation. For ^{1}H, ^{19}F and ^{13}C NMR spectra, the deuterated solvents indicated were used. Mass spectrometric data (MS) were

obtained by electron ionization (EI, 70 eV), chemical ionization (CI, isobutane), or electrospray ionization (ESI, mass analyzer type was ESI-TOF/MS). For preparative scale chromatography, silica gel 60 (0.063-0.200 mm, 70-230 mesh) was used. The solvents for column chromatography were distilled before use.

General procedure for the synthesis of 3-(2-halobenzoyl)chromones. Synthesis of compounds 3a-k: Corresponding enaminone **1** (1 equiv.) and dry pyridine (3 equiv.) successively were weighted and placed in a Schlenk flask (under the flow of dry Ar), equipped with a magnetic stir bar, which then was set with reflux and capped with a rubber septum. Afterwards the dry dichloromethane (10 ml for 1 mmol of enaminone **1**) and corresponding benzoyl chloride **2** (1.1 equiv.) were added *via* a syringe (under the flow of dry Ar), and the reaction mixture was refluxed for 8 h in inert atmosphere (Ar balloon). After the reaction was completed volatiles were evaporated under reduced pressure. The residue was treated with water, filtered, dried in air, and purified by flash column chromatography.

General procedure for the synthesis of 4-quinolone derivatives. Synthesis of compounds 4a-o: Corresponding 3-(2-fluorobenzoyl)chromone **3** (1 equiv.), aliphatic amine (2 equiv.) and K_2CO_3 (2 equiv.) successively were weighted and placed in a pressure tube (under the flow of dry Ar) equipped with a magnetic stir bar. Afterwards the dry DMF (5 ml for 1 mmol of chromone **3**) was added *via* a syringe (under the flow of dry Ar). The pressure tube was capped with a stopper and the reaction mixture was heated at 120 ^oC for 16 h. After the reaction was completed volatiles were removed under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General procedure for hydrolysis of Schiff base. Synthesis of compound 4d': Corresponding 4-quinolone **4d** (1 equiv.) was weighted and placed in a Schlenk flask, equipped with a magnetic stir bar, which then was set with reflux. Afterwards the acetic acid : water 20 : 1 system (10 ml for 1 mmol of 4-quinolone **4d**) was added *via* a syringe, and the reaction mixture was refluxed for 3 h. After the reaction was completed volatiles were removed under reduced pressure. The residue was treated with water, extracted with chloroform, evaporate to dryness and purified by flash column chromatography.

General procedure for the synthesis of benzopyran derivatives. Synthesis of compounds 5a-r, 6a: Corresponding 3-(2-fluorobenzoyl)chromone **3** (1 equiv.), aniline (2 equiv.) and K_2CO_3 (2 equiv.) successively were weighted and placed in a Schlenk flask equipped with a magnetic stir bar, which then was set with reflux. Afterwards the DMF (5 ml for 1 mmol of chromone **3**) was added *via* a syringe. The reaction mixture was heated at 120 ^oC for 16 h. After the reaction was completed volatiles were removed under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General procedure for the synthesis compound 5s: Corresponding 3-(2-fluorobenzoyl)chromone **3c** (1 equiv.), 4,4'-methylenedianiline (0.5 equiv.) and K_2CO_3 (2 equiv.) successively were weighted and placed in a Schlenk flask equipped with a magnetic stir bar, which then was set with reflux. Afterwards the DMF (5 ml for 1 mmol of chromone **3c**) was added *via* a syringe. The reaction mixture was heated at 120 ^oC for 16 h. After the reaction was completed volatiles were removed under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

General procedure for the synthesis of compounds 6b, 7a-e: Corresponding 3-(2-fluorobenzoyl)chromone **3** (1 equiv.), binucleophile (2 equiv.) and K_2CO_3 (2 equiv.) successively were weighted and placed in a pressure tube (under the flow of dry Ar) equipped with a magnetic stir bar. Afterwards the dry DMF (5 ml for 1 mmol of chromone **3**) was added *via* a syringe (under the flow of dry Ar). The pressure tube was capped with a stopper and the reaction mixture was heated at 120 ^oC for 16 h. After the reaction was completed volatiles were removed under reduced pressure. The residue was purified by column chromatography typically using heptane/ethyl acetate mixtures to provide the desired product.

Acknowledgements

Financial support by the DAAD (scholarship for A. G. and S. M.) is gratefully acknowledged. We are grateful to Enamine Ltd. Company (Ukraine) for support. We are grateful to Alexander Hinz for taking part in X-ray analysis and Dr. Dirk Michalik for NMR measurements.

Notes and references

[a] *Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany. E-mail: iva108@gmail.com*
[b] *National Taras Shevchenko University, 62 Volodymyrska st., Kyiv-33, 01033, Ukraine*
[c] *Leibniz-Institut für Katalyse e. V. Universität Rostock Albert-Einstein-Str. 29a, 18059 Rostock, Germany. E-mail: peter.langer@uni-rostock.de*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1. For a comprehensive book and some selected reviews on domino reactions, see: (a) L. F. Tietze, G. Brasche, K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH Verlag GmbH & Co. KGaA, 2006; (b) C. M. R. Volla, I. Atodiresei, M. Rueping, *Chem. Rev.*, 2014, **114**, 2390-2431; (c) X. Zeng, *Chem. Rev.*, 2013, **113**, 6864-6900; (d) A. V. Gulevich, A. S. Dudnik, N. Chernyak, V. Gevorgyan, *Chem. Rev.*, 2013, **113**, 3084-3213; (e) U. Wille, *Chem. Rev.*, 2013, **113**, 813-853; (f) H. Pellissier, *Chem. Rev.*, 2013, **113**, 442-524; (g) N. T. Patil, Y. Yamamoto, *Chem. Rev.*, 2008, **108**, 3395-3442; (h) S. T. Diver, A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317-1382; (i) C. Aubert, O. Buisine, M. Malacria, *Chem. Rev.*, 2002, **102**, 813-834; (j) S. Saito, Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901-2915; (k) K. K. Wang, *Chem. Rev.*, 1996, **96**, 207-222; (l) M. Malacria, *Chem. Rev.*, 1996, **96**, 289-306; (m) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115-136; (n) A. Padwa, M. D. Weingarten, *Chem. Rev.*, 1996, **96**, 223-269; (o) G. H. Posner, *Chem. Rev.*, 1986, **66**, 831-844.
2. For selected reviews on practical application of domino reactions, see: (a) K. E. O. Ylijoki, J. M. Stryker, *Chem. Rev.*, 2013, **113**, 2244-2266; (b) B. B. Toure, D. G. Hall, *Chem. Rev.*, 2009, **109**, 4439-4486; (c) I. Vilotijevic, T. F. Jamison, *Angew. Chem. Int. Ed.*, 2009, **48**, 5250-5281; (d) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger,

Angew. Chem. Int. Ed., 2006, **45**, 7134-7186; (e) R. A. Yoder, J. N. Johnston, *Chem. Rev.*, 2005, **105**, 4730-4756; (f) C. M. Beaudry, J. P. Malerich, D. Trauner, *Chem. Rev.*, 2005, **105**, 4757-4778; (g) K.-i. Takao, R. Munakata, K.-i. Tadano, *Chem. Rev.*, 2005, **105**, 4779-4807; (h) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.*, 1996, **96**, 195-206.

3. For selected reviews on the chemistry of pyrones and related systems, see: (a) A. T. Balaban, D. C. Oniciu, A. R. Katritzky, *Chem. Rev.*, 2004, **104**, 2777-2812; (b) P. J. Brogden, C. D. Gabbutt, J. D. Hepworth, In *Comprehensive Heterocyclic Chemistry*, A. R. Katritzky, C. W. Rees, Eds., Pergamon Press: Oxford, 1984, Vol. 2, p 573.
4. For selected reviews on the chemistry of chromones, see: (a) A. S. Plaskon, O. O. Grygorenko, S. V. Ryabukhin, *Tetrahedron*, 2012, **68**, 2743-2757; (b) G. Sabitha, *Aldrichim. Acta*, 1996, **29**, 15-25; (c) C. K. Ghosh, *J. Heterocycl. Chem.*, 1983, **20**, 1437-1471; (d) H.-J. Kabbe, A. Widdig, *Angew. Chem. Int. Ed.*, 1982, **21**, 247-256.
5. (a) V. O. Iaroshenko, S. Mkrtchyan, A. Gevorgyan, M. Miliutina, A. Villinger, D. Volochnyuk, V. Ya. Sosnovskikh, P. Langer, *Org. Biomol. Chem.*, 2012, **10**, 890-894; (b) V. O. Iaroshenko, I. Savych, A. Villinger, V. Ya. Sosnovskikh, P. Langer, *Org. Biomol. Chem.*, 2012, **10**, 9344-9348; (c) V. O. Iaroshenko, A. Bunescu, A. Spannenberg, L. Supe, M. Milyutina, P. Langer, *Org. Biomol. Chem.*, 2011, **9**, 7554-7558; (d) M. F. Ibad, O.-u.-R. Abid, M. Adeel, M. Nawaz, V. Wolf, A. Villinger, P. Langer, *J. Org. Chem.*, 2010, **75**, 8315-8318; (e) S. Mkrtchyan, V. O. Iaroshenko, S. Dudkin, A. Gevorgyan, M. Vilches-Herrera, G. Ghazaryan, D. M. Volochnyuk, D. Ostrovskyi, Z. Ahmed, A. Villinger, V. Ya. Sosnovskikh, P. Langer, *Org. Biomol. Chem.*, 2010, **8**, 5280-5284.
6. (a) D. M. Volochnyuk, S. V. Ryabukhin, A. S. Plaskon, O. O. Grygorenko, *Synthesis*, 2009, 3719-3743; (b) A. S. Plaskon, S. V. Ryabukhin, D. M. Volochnyuk, K. S. Gavrilenko, A. N. Shivanyuk, A. A. Tolmachev, *J. Org. Chem.*, 2008, **73**, 6010-6013.
7. (a) V. Ya. Sosnovskikh, M. A. Barabanov, B. I. Usachev, *J. Org. Chem.*, 2004, **69**, 8297-8304; (b) V. Ya. Sosnovskikh, M. A. Barabanov, B. I. Usachev, *Org. Lett.*, 2003, **5**, 2501-2504; (c) V. Ya. Sosnovskikh, B. I. Usachev, A. Yu. Sizov, I. I. Vorontsov, Y. V. Shklyaev, *Org. Lett.*, 2003, **5**, 3123-3126.
8. (a) A. Bornadiego, J. Diaz, C. F. Marcos, *Adv. Synth. Catal.*, 2014, **356**, 718-722; (b) Z. Mao, A. Lin, Y. Shi, H. Mao, W. Li, Y. Cheng, C. Zhu, *J. Org. Chem.*, 2013, **78**, 10233-10239; (c) J. Sheng, B. Chao, H. Chen, Y. Hu, *Org. Lett.*, 2013, **15**, 4508-4511; (d) B. Chao, S. Lin, Q. Ma, D. Lu, Y. Hu, *Org. Lett.*, 2012, **14**, 2398-2401; (e) M. A. Terzidis, T. Zarganes-Tzitzikas, C. Tsimenidis, J. Stephanidou-Stephanatou, C. A. Tsoleridis, G. E. Kostakis, *J. Org. Chem.*, 2012, **77**, 9018-9028; (f) Qin, T.; Johnson, R. P.; Porco, Jr. J. A. *J. Am. Chem. Soc.*, 2011, **133**, 1714-1717; (g) H. Dückert, V. Khedkar, H. Waldmann, K. Kumar, *Chem. Eur. J.*, 2011, **17**, 5130-5137; (h) W. Liu, V. Khedkar, B. Baskar, M. Schürmann, K. Kumar, *Angew. Chem. Int. Ed.*, 2011, **50**, 6900-6905; (i) B. Baskar, P.-Y. Dakas, K. Kumar, *Org. Lett.*, 2011, **13**, 1988-1991.
9. (a) V. O. Iaroshenko, S. Mkrtchyan, A. Villinger, *Synthesis*, 2013, 205-218; (b) V. O. Iaroshenko, D. Ostrovskyi, K. Ayub, A. Spannenberg, P. Langer, *Adv. Synth. Catal.*, 2013, **355**, 576-588; (c) V. O. Iaroshenko, I. Knepper, M. Zahid, R. Kuzora, S. Dudkin, A. Villinger, P. Langer, *Org. Biomol. Chem.*, 2012, **10**, 2955-2959.
10. (a) R. Weiss, M. Bess, S. M. Huber, F. W. Heinemann, *J. Am. Chem. Soc.*, 2008, **130**, 4610-4617; (b) C. P. Jones, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 7968-7973; (c) D. Zewge, C.-y. Chen, C. Deer, P. G. Dormer, D. L. Hughes, *J. Org. Chem.*, 2007, **72**, 4276-4279; (d) P. Hradil, M. Grepl, J. Hlavac, M. Soural, M. Malon, V. Bertolasi, *J. Org. Chem.*, 2006, **71**, 819-822; (e) N. Haddad, J. Tan, V. Farina, *J. Org. Chem.*, 2006, **71**, 5031-5034.
11. For selected reviews on 4-quinolone based antibiotics and biologically important compounds, see: (a) H. Huse, M. Whiteley, *Chem. Rev.*, 2011, **111**, 152-159; (b) Q. Li, L. A. Mitscher, L. L. Shen, *Med. Res. Rev.*, 2000, **20**, 231-293; (c) S. W. Pelletier, (ed.). *Alkaloids, Chemical and Biological Perspectives*, Volume 6, Wiley-VCH, 1988, p542, ISBN-10: 0-471-60298-1; (d) R. B. Silverman, *The organic chemistry of drug design, and drug action* (Second Edition), Elsevier Academic Press, 2004, p617, ISBN 0-12-643732-7; (e) J. Fischer, C. R. Ganellin, *Analogue-based Drug Discovery* (First Edition), Wiley-VCH, 2006, p575, ISBN: 3-527-31257-9; (f) L. P. Graham, *An Introduction to Medicinal Chemistry* (Forth Edition), Oxford University Press, 2009, p776, ISBN: 978-0-19-923447-9; (g) G. Collin, H. Höke, *"Quinoline and Isoquinoline" Ullmann's Encyclopedia of Chemical Technology*, Wiley-VCH, 2005, doi:10.1002/14356007.a22_465.
12. For selected reviews on Buchwald-Hartwig amination, see: (a) D. S. Surry, S. L. Buchwald, *Chem. Sci.*, 2011, **2**, 27-50; (b) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2008, **47**, 6338-6361; (c) J. F. Hartwig, *Acc. Chem. Res.*, 2008, **41**, 1534-1544; (d) J. P. Wolfe, S. Wagaw, J.-F. Marcoux, S. L. Buchwald, *Acc. Chem. Res.*, 1998, **31**, 805-818; (e) J. F. Hartwig, *Angew. Chem. Int. Ed.*, 1998, **37**, 2046-2067.
13. For selected reviews on Cu-catalyzed Ullmann amination, see: (a) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev.*, 2014, **43**, 3525-3550; (b) J. Bariwal, E. Van der Eycken, *Chem. Soc. Rev.*, 2013, **42**, 9283-9303; (c) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.*, 2003, **42**, 5400-5449.
14. For selected reviews on nucleophilic aromatic substitution and leaving groups, see: (a) F. Terrier, *Modern Nucleophilic Aromatic Substitution*, Wiley-VCH, Weinheim, 2013, ISBN: 9783527318612; (b) M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (Sixth Edition), John Wiley & Sons, Inc., 2006, p853, ISBN: 9780470084960; (c) M. P. Drapeau, T. Ollevier, M. Taillefer, *Chem. Eur. J.*, 2014, **20**, 5231-5236; (d) M. Liljenberg, T. Brinck, B. Herschend, T. Rein, S. Tomasi, M. Svensson, *J. Org. Chem.*, 2012, **77**, 3262-3269; (e) H. Amii, K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119-2183.
15. For selected reviews on silicon-based Lewis acids and water scavengers, see: (a) D. M. Volochnyuk, S. V. Ryabukhin, A. S. Plaskon, O. O. Grygorenko, *Synthesis*, 2009, 3719-3743; (b) A. D. Dilman, S. L. Ioffe, *Chem. Rev.*, 2003, **103**, 733-772.
16. For selected reviews on naturally occurring benzopyrans, see: (a) G. Berkovic, V. Krongauz, V. Weiss, *Chem. Rev.*, 2000, **100**, 1741-1753; (b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893-930; (c) J.-M. Gao, S.-X. Yang, J.-C. Qin, *Chem. Rev.*, 2013, **113**, 4755-4811; (d) R. Pratap, V. J. Ram, *Chem. Rev.*, 2014, **114**, 10476-10526.
17. For a comprehensive book and some selected reviews on ring-chain tautomerism, see: (a) L. Lazar, F. Fülöp, *Eur. J. Org. Chem.*, 2003, 3025-3042; (b) R. E. Valters, W. Flitsch, *Ring-Chain Tautomerism*, A. R. Katritzky (ed.), Plenum Press, New York, 1985, ISBN: 978-1-4684-4885-6; (c) P. R. Jones, *Chem. Rev.*, 1963, **63**, 461-487.
18. F. M. Dean, K. B. Hindley, S. Small, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2007-2010.
19. X-Ray Crystallographic data (excluding structure factors) for the structure **3e**, **4a**, **4b**, **4j**, **4l**, **7a**, **7c**, **7e** and **9a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 1016268-1016274, 868712 and 1019513 can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk, or *via* www.ccdc.cam.ac.uk/data_request/cif.