Reagent-controlled domino synthesis of skeletally-diverse compound collections†

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An efficient reagent-controlled methodology for generating highly substituted diverse scaffolds from a common substrate has been developed; thus, treatment of a common precursor with different desilylating reagents, such as ammonium fluoride, caesium fluoride and PPTS, triggers different domino reaction sequences, yielding highly substituted pyridines, phenols and benzopyrans, respectively; the substituent patterns of these scaffolds provide further opportunities for library development.

The use of diverse sets of small molecules in chemical biology studies has led to new insights into various biological phenomena.[1–6] For the development of such compounds, Diversity-Oriented Synthesis (DOS)[4] and Biology-Oriented Synthesis (BIOS)[5,6] of compound collections are efficient approaches. In both approaches, structural complexity and diversity is often generated by means of multi-step sequences employing skeletally-differentiating transformations of common precursors. Here we report on the development of new structurally-diversifying domino reaction[7] sequences, giving access to highly substituted pyridines, benzopyrans or phenols from a common intermediate.

Substrates capable of entering domino sequences must have diverse reactive sites, at which different chemical reactions can take place in a sequential manner. We envisioned employing appropriately substituted 3-chromanylidene-β-ketoesters **1** (Fig. 1) as key intermediates for the establishment of new domino sequences. These compounds contain electrophilic centers, *e.g.* C2 and C1′, where nucleophiles can attack, and also nucleophilic centers such as C4′ and OH (after deprotection). Furthermore, the C3′ ketone provides an entry into imine–enamine chemistry. Moreover, desilylating the alcohol at C7′ could possibly induce the formation of six-membered hemiacetals. Thus, these substrates can potentially enter into various different reaction pathways. Initially, we planned to desilylate the alcohol and determine if the formation of hemiacetals is followed by further reactions at the different electrophilic centers available in these molecules. Using the standard desilylating reagent tetrabutylammoniumfluoride (TBAF) led to a retro-aldol reaction, thereby hydrolyzing **1** to formylchromone and β-ketoesters.

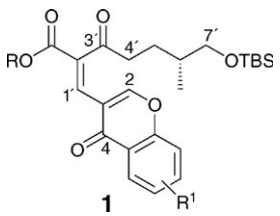

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Fig. 1 Substrate for domino reactions with diverse reactive sites.

Attempted *tert*-butyldimethylsilyl (TBS) deprotection of **1** using TBAF under dry conditions was also unsuccessful. Upon employing another desilylating reagent, *i.e.* ammonium fluoride, at room temperature, single products were formed (TLC control) within an hour, which after purification (silica gel column chromatography) were identified by spectroscopic techniques (NMR, DEPT, HRMS) to be pyridines **4** (Scheme 1).[8]

Under these reaction conditions, the TBS ether remained intact (**4**, Scheme 1). Extending the reaction time and raising the temperature (60 °C) led to clean removal of the protecting group (**1** → **5**; Scheme 1). Further, saponification of the esters with 1 M NaOH provided the corresponding substituted pyridine carboxylic acids (**6**, Scheme 1; for a tabular survey of the synthesized compounds see the ESI†).

Chromanylidene-β-ketoesters **7** with short alkyl chains (R^4 = Me or H) were also cleanly transformed to the corresponding substituted pyridines **8** by means of the domino route described above. The corresponding pyridine carboxylic acids, **9**, were obtained after hydrolysis of the esters with 1 M NaOH (Scheme 1). Formation of the pyridine ring proceeded, most likely, by means of the initial conversion of *e.g.* β-ketoester **1** into enamine **2**, which then attacks the activated C-2 position in the chromone (**2**→**3**, Scheme 1). Rearrangement was accompanied by opening of the chromone, and aromatization resulted in the formation of pyridine **4**. Overall, this domino sequence provided high yields of substituted pyridines (see the ESI†).

The reactions detailed above demonstrate that electrophilic centers, especially C2 (Fig. 1), can be easily attacked by nucleophiles in a sequential way. So as to determine whether an alkoxide, generated by the desilylation of **1**, attacks at C2 or triggers other cascade processes, we used CsF as a desilylating reagent. Thus, chromanylidene intermediates **1** and **7** were

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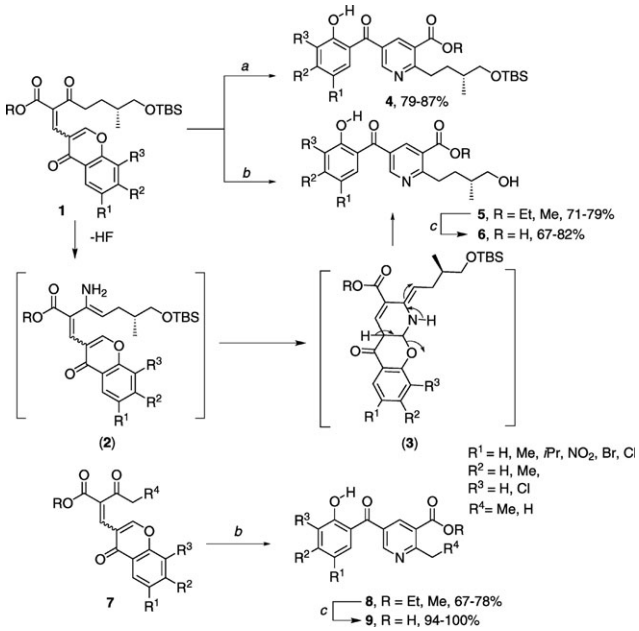
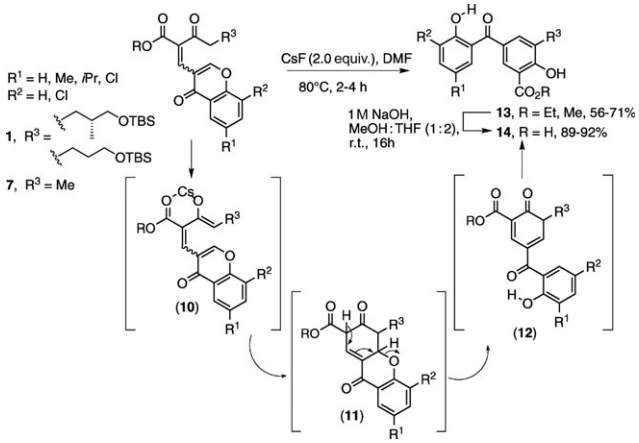


Scheme 1 Domino synthesis of substituted pyridines: (a) NH_4F (10.0 equiv.), MeOH, r.t., 1–3 h; (b) NH_4F (10.0 equiv.), MeOH, 60 °C, 6–10 h; (c) 1 M NaOH, MeOH/THF (1 : 2), r.t., 16 h.

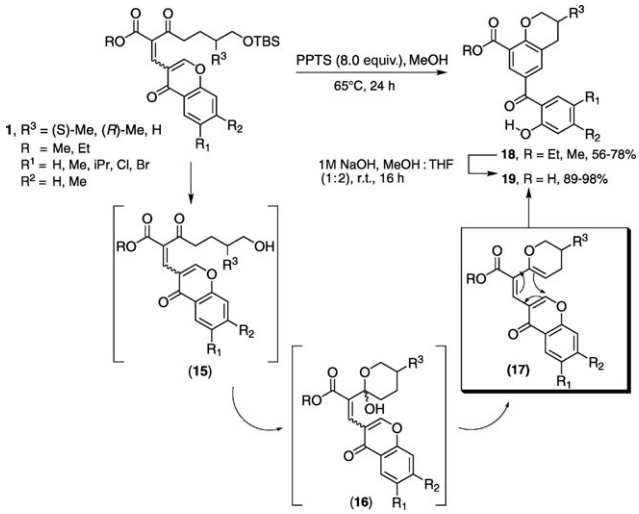
treated with CsF in DMF. Interestingly, we observed the formation of substituted phenols **13** under these reaction conditions in moderate to good yields (see the ESI for a tabular survey of the results†).

At least two equivalents of CsF were required to obtain good to excellent yields of **13**. Again, hydrolysis of the ester moiety in the products yielded carboxylic acids **14** in high yields (Scheme 2). Mechanistically, a caesium enolate may have been formed after removal of the TBS group and added to C2 of the chromone, forming a C–C bond (**10**→**11**, Scheme 2). Subsequent ring opening (**11**→**12**) and aromatization gave rise to phenols **13**, which were obtained in deprotected forms (Scheme 2).

These two domino processes (Scheme 1 and Scheme 2) provided highly substituted phenols and pyridines, which could be further diversified for compound collection synthesis. However, we did not observe the expected hemiacetal formation from substrate **1**. To enter such a reaction pathway, a desilylating reagent may be required that provides conditions suitable for acetal formation. Based on this assumption pyridinium *para*-toluene sulfonate (PPTS) was employed as the desilylating reagent. Interestingly, treatment of silyl ethers **1** with PPTS in methanol at 65 °C for 36 h led to the formation of benzopyrans **18** (Scheme 3). However, transesterification of the substrates occurred, which could be successfully avoided by reducing the reaction time to 24 h. This finding provided another cascade route to a different scaffold, around which a new compound collection could be readily generated. As in the cases described above, the hydrolysis of the ester groups with sodium hydroxide provided the corresponding carboxylic acids in good yields.



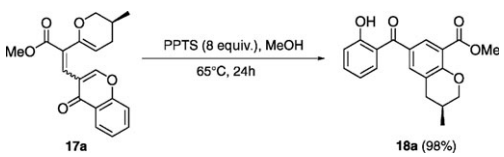
Scheme 2 Domino synthesis of substituted phenols.



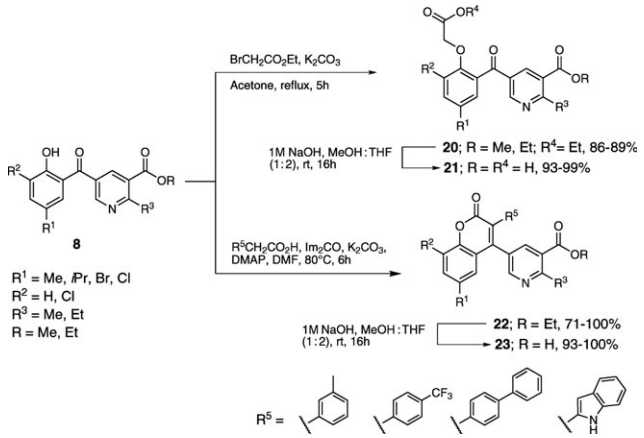
Scheme 3 Domino synthesis of benzopyrans.

Under these reaction conditions, the TBS group is removed, and the liberated alcohol **15** cyclizes to the ketone, yielding the expected hemiacetal **16** (Scheme 3), which eliminates water to form the dihydropyran **17**. An intramolecular cyclization followed by aromatization leads to benzopyrans **18**. This domino sequence provides a clear advantage over the reported multi-step synthesis of similar molecules, which involves the generation of 1,3-bis(trimethylsilyloxy)-7-chlorohepta-1,3-dienes (3 steps) followed by additional steps to yield benzopyrans.[9]

To gain further insight into the reaction mechanism, the reaction between **1** (R^3 = (*S*)-Me) and PPTS in methanol was stopped after 1 h, and the major product quickly purified by flash column chromatography. Interestingly, the product obtained in this case was not the benzopyran but the chromanomethylidene-substituted dihydropyran **17a** (Scheme 4), which appears to be the precursor of the benzopyran (Scheme 3). Stirring **17a** under the same reaction conditions, *i.e.* with PPTS in methanol at 65 °C for 24 h, yielded exclusively the



Scheme 4 From dihydropyran to benzopyran.



Scheme 5 Diversification of substituted pyridine molecules.

corresponding benzopyran **18a**, thus confirming the intermediacy of dihydropyrans.

The skeletally-differentiating domino approach described above provided molecules with various functionalities, which could be explored for adding further diversity to the compound collections. To this end, the phenol moiety in substituted pyridines **8** was converted to intermediate esters **20** by treatment with bromoacetic acid esters. Saponification of **20** yielded the pyridine dicarboxylic acids **21** in good yields (Scheme 5). Coumarin, as a ''privileged'' scaffold, shows multiple biological properties, especially anti-HIV and antibiotic activities.[10] To add this scaffold to the molecular architecture of the library, the substituted pyridines **8** were readily converted to the coumarin-substituted pyridine carboxylates by a one pot procedure (see the ESI†). Alkylation of **8** with diverse acetic acids, followed by a base-mediated condensation, yielded the desired coumarin-substituted pyridine carboxylates **22**, and subsequent saponification led to the corresponding acids **23** (Scheme 5).

In conclusion, we have discovered efficient reagent-controlled domino processes that led to structurally-diverse functionalized molecules in a complementary manner. The general approach to synthesizing different compound collections from a common intermediate by control with different reagents should provide efficient access to collections of small molecules for chemical biology and medicinal chemistry research.

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