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Direct synthesis of γ-pyrones by electrophilic condensation of β-ketoesters†

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Triflic anhydride is a versatile electrophile that is able to activate poor nucleophiles. Herein, we show that readily available β-keto esters are activated by Tf_2O furnishing γ-pyrones. Mechanistic studies suggest that this transformation proceeds *via* a double triflation, formation of an oxocarbenium intermediate and dealkylation promoted by a crucial nitrile additive.

Introduction

Triflic anhydride (Tf_2O) is a versatile electrophile in organic chemistry, commonly used to generate triflate moieties with exceptional leaving group ability.[1] Its electron-poor character makes it prone to react with relatively weak nucleophiles such as carbonyl groups, non-activated arenes and unsaturated compounds, ethers or nitriles, and thus initiate a series of interesting transformations.[1] Our group and others are well aware of the peculiar reactivity of Tf_2O and reported several examples of Tf_2O-mediated domino electrophilic rearrangements for the construction of diverse scaffolds.[2–14]

γ-Pyrones have the general structure depicted in Fig. 1(a) and form the basic skeleton of various biologically relevant substances.[15] These compounds are also key intermediates in the synthesis of pyridinone derivatives (Fig. 1(b)) that present relevant pharmaceutical activity[16] and are used as fluorescent probes.[17,18] These scaffolds are usually synthesized by three general pathways (Fig. 1(c)): cyclocondensation of 1,3,5-tricarbonyl compounds under acidic conditions,[19,20] hetero Diels–Alder reaction between a ketoketene and an alkyne[21] or recyclisation of α-pyrones.[22] All these strategies imply some synthetic effort for the synthesis of the non-commercially available starting materials.

Herein we report a triflic anhydride-mediated condensation of β-ketoesters resulting in the direct synthesis of γ-pyrones.

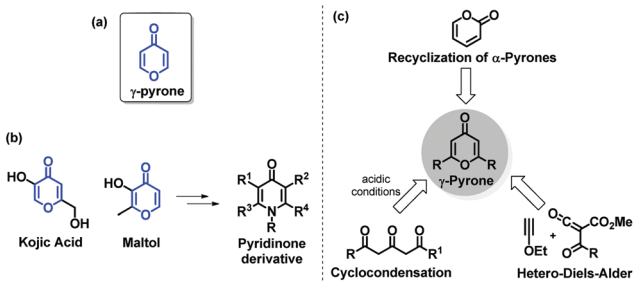
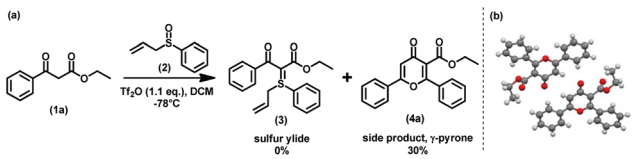


Fig. 1 (a) General structure of γ-pyrones, (b) natural products with a γ-pyrone scafold and application, (c) synthetic methods to access γ-pyrones.

Results and discussion

During our studies on the chemistry of sulfur ylides,[23] we required access to an ylide (**3**) containing a specific substitution pattern on sulfur (Scheme 1(a)). An attempt to synthesize this ylide by combination of the corresponding β-ketoester (**1a**) and the sulfoxide (**2**) unexpectedly afforded a new product that was identified as γ-pyrone (**4a**). Spectroscopic features include a well-defined singlet peak in ^1H NMR spectra at 6–7 ppm, but ultimately an unambiguous structural assignment was made possible by single crystal X-ray analysis (Scheme 1(b)).



Scheme 1 (a) Original observation on the Tf_2O-mediated condensation of β-ketoesters. (b) X-ray analysis of the side product γ-pyrone (**4a**).

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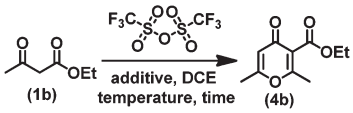
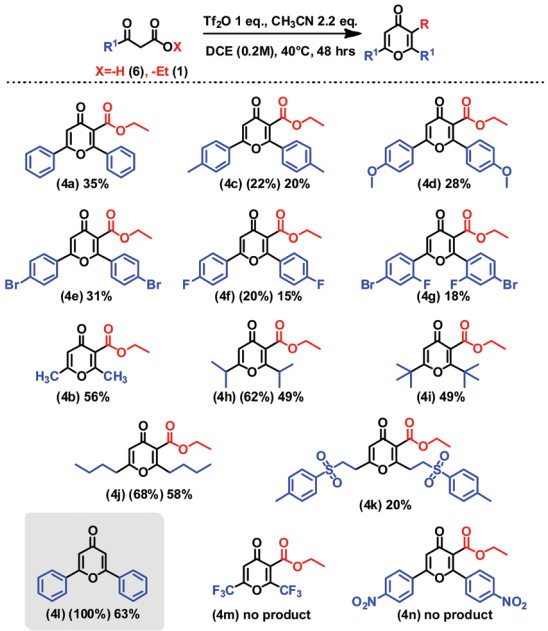
Table 1 Optimization of the reaction conditions



Entry	Tf_2O (eq.)	Temp. (°C)	Conc. (M)	Additive (eq.)	Time (h)	NMR yield
1	1	23	0.22	None	48	No product
2	1	40	0.22	None	48	37%
3	1	40	0.22	CH_3CN (2.2)	48	59%
4	1	40	0.22	CH_3CN (2.2) TfOH (0.2)	48	49%
5	1	40	0.22	TfOH (0.2).	48	23%
6	1	40	0.22	CH_3CN (2.2)	18	42%
7	1	40	0.22	CH_3CN (2.2)	7 days	59%
8	1	40	0.22	CH_3CN (2.2) (air)	48	58%
9	1	40	0.22	EtCN (2.2)	48	53%
10	1	40	0.22	*t*-BuCN (2.2)	48	55%
11	1	40	0.22	CCl_3CN (2.2)	48	25%
12	2	40	0.22	CH_3CN (3)	48	47%
13	2	40	0.22	CH_3CN (4)	48	37%



Scheme 2 Substrate scope of the Tf_2O-mediated condensation of β-ketoesters (in brackets are the yields determined by NMR).

This unanticipated result compelled us to explore and optimize the conditions for the synthesis of γ-pyrones from β-ketoesters.

Early control experiments (not depicted) revealed that the sulfoxide component is not needed for the successful reaction described above. As depicted in Table 1, we set to investigate the condensation of model β-ketoester (**1b**) in the presence of triflic anhydride, and first studied the influence of temperature. At 23 °C no product was observed after 48 hours (Table 1, entry 1). However, increasing the temperature to 40 °C resulted in a 37% yield (NMR analysis) of γ-pyrone (Table 1, entry 2).

Subsequently, the influence of additives was screened. While with DMSO no product was observed (see ESI†), 59% yield was obtained by adding 2.2 eq. of MeCN (Table 1, entry 3). This observation is in accordance with what was previously observed by Martinez *et al.*[24]

The impact of triflic acid was also studied. The yield decreased when only 0.2 eq. of this reagent was added, both in the presence and absence of MeCN (Table 1, entries 4 and 5). When the reaction was quenched after 18 hours only 42% yield was observed, but on extending the reaction time up to 7 days no improvement was observed (59%) (Table 1, entries 6 and 7). This reaction could also be run in an open vessel with virtually no change in yield (Table 1, entry 8).

The influence of the nitrile was also studied and it became clear that electron-poor nitriles are less reactive than electron-rich ones, suggesting a possible nucleophilic role in the mechanism (Table 1, entries 9–11).

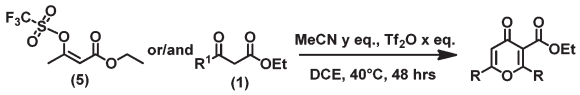
An extensive screening of the Tf_2O : MeCN ratio was finally carried out (summarised in Table 1, entries 12 and 13), and the best overall conditions for this transformation comprise the use of 1 eq. of Tf_2O and 2.2 eq. of MeCN at 40 °C over 48 hours.

With improved conditions in hand, we examined the substrate scope of this transformation (Scheme 2).

The γ-pyrone products were obtained in yields up to 100% using different substrates. Alkyl β-ketoesters appear to be more reactive under these conditions (up to 68% yield) than the corresponding aryl derivatives (up to 28% yield). Substrates carrying electron-withdrawing groups are not reactive under this protocol resulting in the recovery of the starting material (Scheme 2, **4m** and **4n**). An interesting result was obtained when a β-ketoacid (benzoylacetoacetic acid) was used instead of the ester, affording the disubstituted γ-pyrone in quantitative yield (Scheme 2, **4l**).

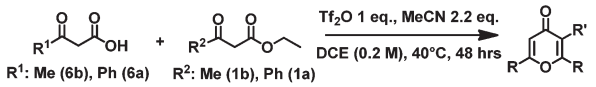
At this juncture, some preliminary mechanistic studies were carried out and the results thereof are compiled in Table 2. We initially hypothesized that this transformation might proceed *via* the intermediacy of an enol triflate (**5**) derivative. Such an enol triflate could be prepared independently.[25] When this substrate was subjected to the reaction conditions without Tf_2O, in both the presence and absence of MeCN, no product was observed (Table 2, entries 2–4). Hypothesizing an equilibrium scenario, we employed a 1 : 1 mixture of enol triflate and β-ketoester, but even in the presence of 1 eq. of Tf_2O this resulted in only 5% of γ-pyrone (**4b**) (Table 2, entry 5). When the same substrate mixture was treated under the optimized conditions (with MeCN) the γ-pyrone (**4b**) was obtained in 21% yield (Table 2, entry 6). Albeit a positive outcome, this is a rather low yield compared to the standard reaction (*vide supra*). To clarify this strange result, the same experiment was repeated but using a different β-ketoester (ethyl benzoylacetate (**1a**)) with the same enol triflate (**5**) previously employed. In fact this experiment resulted in 20% yield of **4a**, showing that the enol triflate is not the active intermediate in this transformation.

Table 2 Mechanistic studies with enol triflate



Entry	(5)	(1)	MeCN	Tf_2O	NMR yield
1	None	(**1b**)	2.2 eq.	1 eq.	59%
2	1 eq.	—	—	—	No product
3	1 eq.	—	2.2 eq.	—	No product
4	0.5 eq.	(**1b**) 0.5 eq.	—	—	No product
5	0.5 eq.	(**1b**) 0.5 eq.	—	1 eq.	(**4b**) 5%
6	0.5 eq.	(**1b**) 0.5 eq.	2.2 eq.	1 eq.	(**4b**) 21%
7	0.5 eq.	(**1a**) 0.5 eq.	2.2 eq.	1 eq.	(**4a**) 20%

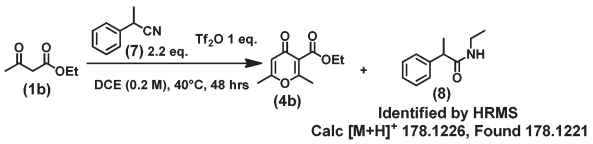
Table 3 Mechanistic studies using β-ketoacids



Entry	β-Ketoacid	β-Ketoester	Product	NMR yield
1	(**6b**) 0.5 eq.	(**1b**) 0.5 eq.	(**4b**)	44%
2	(**6b**) 0.5 eq.	(**1a**) 0.5 eq.	(**4a**)	16%
3	(**6a**) 0.5 eq.	(**1a**) 0.5 eq.	(**4a**)	50% (49%)[a]
4	(**6a**) 1 eq.	—	(**4l**)	No MeCN, 100%

[a] Isolated yield.

Along with the surprising result previously obtained with a β-ketoacid substrate (Scheme 2, **4l**), additional experiments were triggered by these observations. When a mixture of acetoacetic acid (**6b**) and the corresponding ethyl ester (**1b**) is subjected to the optimized conditions, a 44% yield of γ-pyrone (**4b**) (Table 3, entry 1) ensues. Conversely, a mixture of (**6b**) and (**1a**) gave 16% of (**4a**) (Table 2, entry 2) whilst a 50% yield of



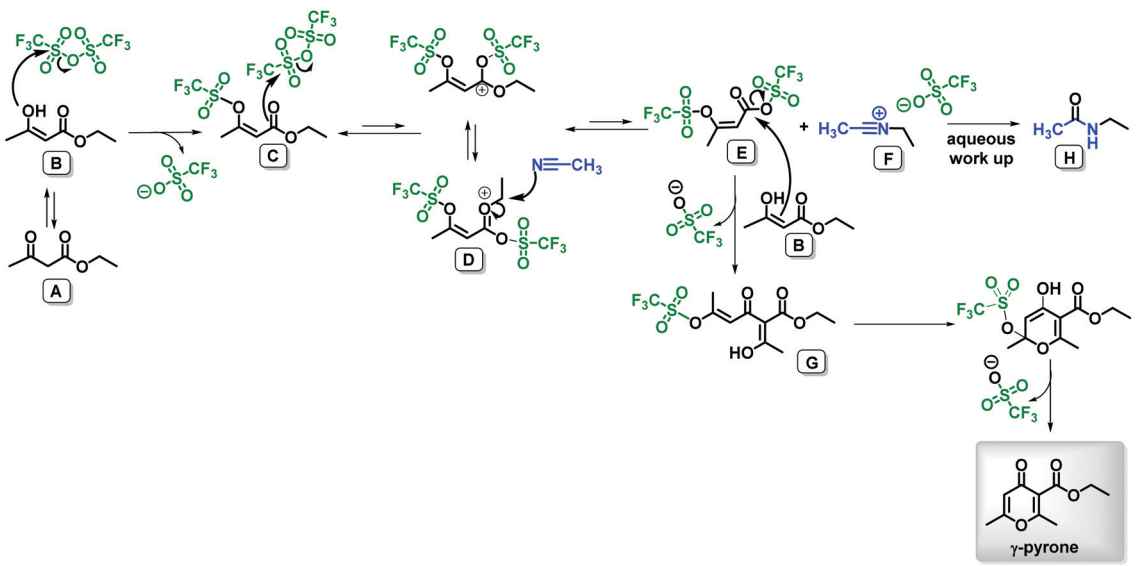
Scheme 3 Tf_2O-mediated condensation of β-ketoester (**1a**) using 2-phenylpropanenitrile (**7**).

the same γ-pyrone (**4a**) is obtained if a mixture of (**6a**) and (**1a**) is used (Table 2, entry 3). This last experiment provides a higher yield of **4a** than that using only the corresponding β-ketoester (**1a**) (Scheme 2, **4a**), indicating that a second triflation must be present in the mechanism which is faster for the carboxylic acid substrate. This conclusion is also supported by another experiment when **6a** was subjected to the optimized conditions but without MeCN resulting in a quantitative yield of the corresponding 2,6-diphenyl-4*H*-pyran-4-one **4l**, which also supports the hypothesis of the nucleophilic role of MeCN in this transformation, mentioned above.

To verify the role of the nitrile in the reaction under study, we performed an experiment using the optimized conditions and the model β-ketoester (**1b**) but replacing acetonitrile by 2-phenylpropanenitrile (**7**) (Scheme 3). In fact, after work-up we were able to identify amide (**8**) in the crude by high resolution mass spectrometry. This confirms the nucleophilic role of the nitrile as the ultimate destiny of the ethyl group from the β-ketoester.

Taking into account the results described above, we can postulate the mechanism depicted in Scheme 4.

In solution, the β-ketoester **A** is in equilibrium with the corresponding enol **B** which can afford the enol triflate **C** in the presence of Tf_2O. At high temperature, this species can undergo a second triflation resulting in oxocarbenium **D**



Scheme 4 Proposed mechanism for the synthesis of γ-pyrones by electrophilic condensation of β-ketoesters.

which is prone to nucleophilic dealkylation (promoted by MeCN). This step gives the nitrilium ion **F** – which following aqueous work up leads to the corresponding amide **H** – and intermediate **E**, which is now a strong acylating agent. Acylation of another molecule of enol **B** with **E** generates species **G**, primed for intermolecular cyclization (Michael addition/elimination) finally affording the γ-pyrone.

Conclusions

In summary, we have reported a triflic-anhydride-mediated direct condensation of β-ketoesters to afford γ-pyrones. This transformation allows expedient and simple access to the γ-pyrone framework, delivering the products in moderate yields. Mechanistic experiments suggest the formation of a bis-electrophilic species.

Acknowledgements

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