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Beyond the Five and Six: Evaluation of Seven-Membered Cyclic Anhydrides in the Castagnoli–Cushman Reaction

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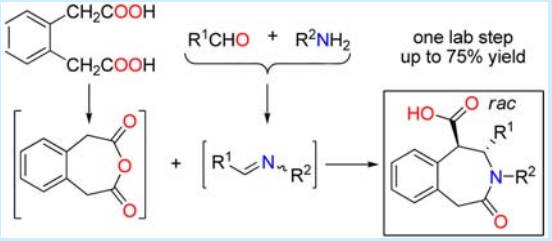
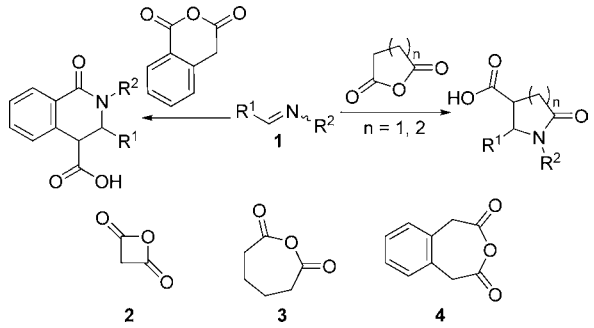
Supporting Information

ABSTRACT: The Castagnoli–Cushman reaction with benzo[*d*]-oxepine-2,4(1*H*,5*H*)-dione as an anhydride component allowed for preparation of 2,3-disubstituted 4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]-azepine-1-carboxylic acids in 21–75% yields and with good *trans* diastereoselectivity. The method worked with imines generated from aromatic or α-branched aliphatic aldehydes and is amenable for both parallel synthesis and scale-up. The procedure for epimerization of the resulting *trans*-disubstituted tetrahydrobenzo[*d*]azepines to their *cis* isomers was also developed.



Thorough exploration of the chemical space relevant for medicinal chemistry requires synthetic methods that open access to potential lead compounds in an efficient manner.[1] Multicomponent reactions are especially promising in this view since they provide sufficient diversity of the compound libraries with minimum synthetic efforts required.[2] In particular, the Castagnoli–Cushman reaction (CCR), i.e., a reaction of imines (**1**) with cyclic andydrides (Scheme 1),[3] has been considered as

Scheme 1



an efficient tool for the synthesis of pyrrolidones and piperidones as well as their fused and heteroatom-substituted analogues.[4] Unlike many other multicomponent reactions, the CCR leads to the formation of nonflattened sp^3-enriched cores; therefore, it is well-compatible with the concept of lead-oriented synthesis.[5]

To date, the use of the CCR has been limited to the construction of five- and six-membered heterocycles. Four-membered rings are unlikely to be obtained by this reaction due to instability of malonic anhydride (**2**). On the contrary, cyclic systems of larger size such as seven-membered rings could be in principle formed in the CCR since adipic anhydride (**3**) and its corresponding benzo analogue (**4**) are known and stable compounds.[6] Meanwhile, azepanes that can form in such CCR are in the top 100 most frequently used ring systems in small molecule drugs.[7] For example, the tetrahydrobenzoazepine derivative ivabradine (**5**) was approved by the FDA in 2015 for the symptomatic management of stable angina pectoris, fenoldopam (**6**) in 1997 as an antihypertensive agent, and lorcaserin (**7**) in 2012 as an antiobesity drug (Figure 1).[8] Among other examples, a candidate drug against Alzheimer's disease, semagacestat (**8**), which has reached Phase III clinical studies, can be mentioned.[9]

In this work, we describe evaluation of the seven-membered cyclic anhydrides **3** and **4** in Castagnoli–Cushman reaction for the construction of seven-membered rings, namely, azepane and tetrahydrobenzo[*d*]azepine derivatives. The anhydrides **3** and **4** were prepared from the corresponding dicarboxylic acids using modified literature procedures.[6,10] It should be noted that adipic anhydride is known to be formed in its polymeric form (**9**), which can be transformed into cyclic (**3**) upon heating. Since isolation of pure **3** by vacuum distillation of **9** gives low yields of the target product (32%), we checked both **3** and **9** in the CCR with imine **1a** (xylene, 140 °C, 20 h). Although no target product **10** was detected in the reaction mixtures, they were shown to be nearly identical by LCMS.

Moreover, heating of **3** in xylene at 140 °C resulted in its conversion to **9** (after 3.5 h, the **3** to **9** ratio was 0.8:1 according to ^{1}H NMR). The reverse reaction was slower: a sample of **9** showed 4% conversion to **3** under the same conditions. Therefore, the polymeric form **9** is obtained from **3** upon

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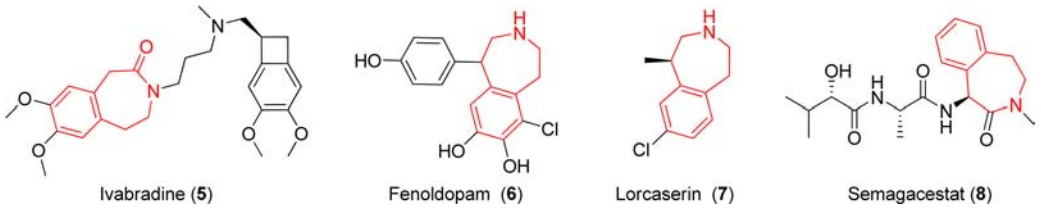


Figure 1. Biologically active tetrahydrobenzo[*d*]azepines.

Scheme 2

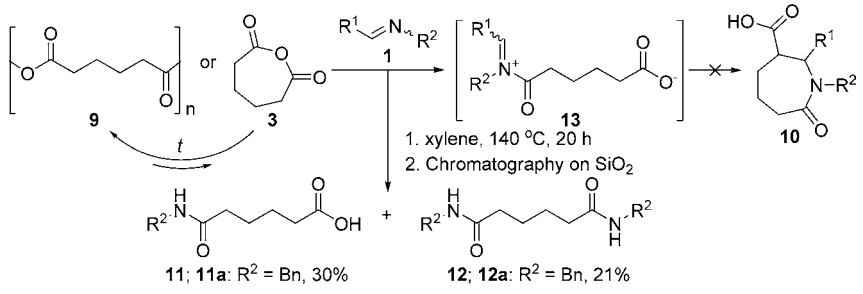
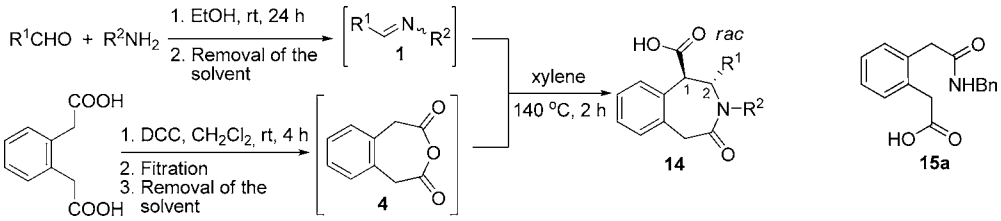


Table 1. Reaction of Imines 1a–j with Anhydride 4



no.	imine	R^1	R^2	product	yield (%)	$J(H^1–H^2)$ (Hz)
1	**1a**	Ph	Bn	**14a**	71[a]	9.5
2	**1b**	Ph	Me	**14b**	75[a]	9.1
3	**1c**	Ph	Ph	**14c**	52	8.8
4	**1d**	4-pyridyl	Bn	**14d**	71	8.3
5	**1e**	Ph	2,4-$(MeO)_2C_6H_3$	**14e**	71	9.3
6	**1f**	4-$MeOC_6H_4$	Bn	**14f**	74	10.0
7	**1g**	*t*-Bu	Bn	**14g**	57	8.8
8	**1h**	*i*-Pr	Bn	**14h**	31[a]	6.5
9	**1i**	*i*-Pr	2,4-$(MeO)_2C_6H_3$	**14i**	28	6.3
10	**1j**	Me	Bn	**14j**	0[a]	

[a]Reaction was performed with presynthesized imine.

heating, and we used **9** in further experiments performed at high temperatures.

Unfortunately, none of the conditions evaluated for the reaction of adipic anhydride (**9** or **3**) with imines **1a–c** gave the target products **10** (see Table S1). Since all of the crude reaction mixtures showed similar patterns in LCMS and ^{1}H NMR, we performed chromatographic separation only with two of them. It was shown that amides **11** and **12** were the main products isolated (Scheme 2). We believe that the intermediate zwitterion **13** was not reactive enough to give the product of cyclization **10**.

We also performed reaction of the monomeric adipic anhydride (**3**) with the imine **1a** in $CHCl_3$ at rt; under these conditions, the target product **10** was not obtained.

After the negative results obtained with adipic anhydride, we turned our attention to its benzo analogue **4**. Compound **4** is a seven-membered analogue of homophthalic anhydride (which is well-studied in the CCR) and hence should be far more reactive than **3** due to increased CH acidity of the corresponding zwitterionic intermediate. The expected product **14b** was obtained as a single diastereomer in 75% yield under standard thermodynamically controlled CCR conditions (xylene, 140 °C, 2 h). Relative *trans* configuration of the compound **14b** was established using X-ray single-crystal diffraction studies.[11]

Inspired by this result, we studied series of imines **1a–i** in the reaction with **4** under the conditions mentioned above (Table 1). It was found that in the case of imines derived from nonenolizable aldehydes the products **14a–g** were obtained in 52–75% yields as *trans* diastereomers. We have shown that both imines **1** and anhydride **4** can be generated and used without any purification; only filtration (in the case of **4**) and removal of the solvent (in both cases) were needed. This makes the method compatible with parallel synthesis conditions. Moreover, this procedure was amenable to scale-up: ∼10 g of the product **14e** was obtained a single run.

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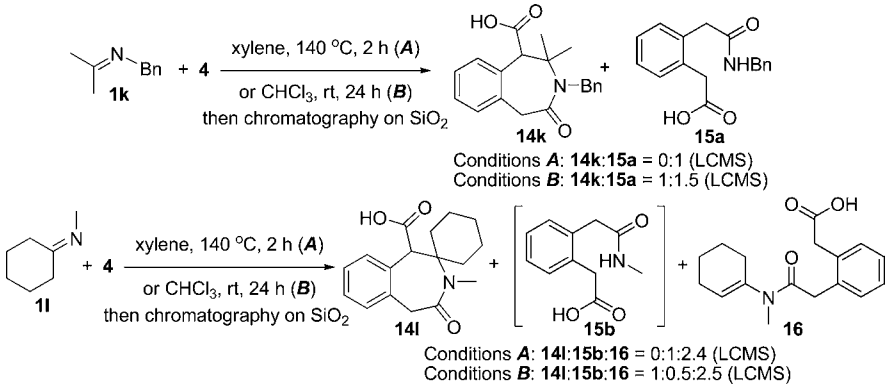
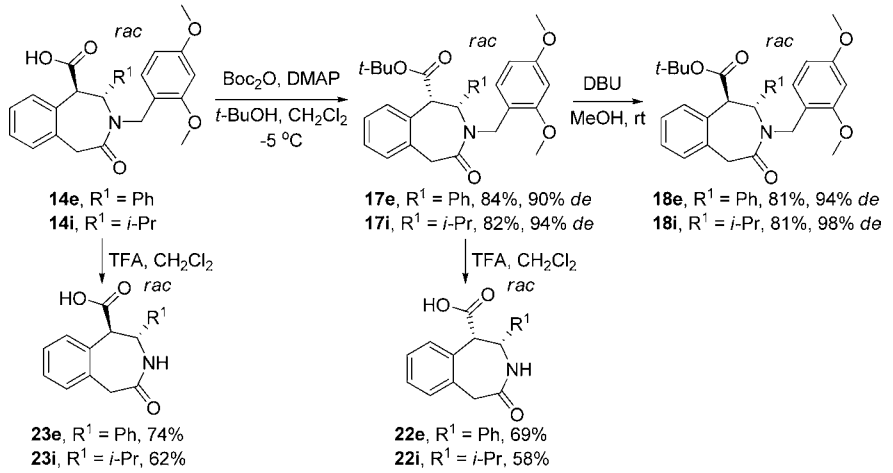
Scheme 3



Scheme 4



In the case of the imines **1h,i** derived from an enolizable α-branched aldehyde, the yields of the products **14h,i** were moderate (28−31%). In the case of **14h**, we could identify amide **15a** (∼10% by LCMS) as one of the numerous byproducts. In the case of the imine **1j** derived from acetaldehyde, the target compound **10j** was not formed at all; the compound **15a** was the major product isolated in this case. These results can be possibly explained by the formation of *N*-acylenamine byproducts and their further transformations, which is well-documented for other anhydrides.[3c]

The relative stereochemistry of the products **14b−i** was confirmed by $J(H^1-H^2)$ (6.3−10.0 Hz) (Table 1); these large values are in accordance with the *trans* orientation of the corresponding protons in a pseudoaxial position ($H^1-C^1-C^2-H^2$ torsion angle close to 180°), which is observed in the crystalline state for **14b**. Notably, these values are different from those observed for the six-membered analogues, where the corresponding protons are in pseudodiequatiorial position.[12]

We studied the possibility of improving the yields of **4** with **14h** in $CHCl_3$ at rt led to a complex mixture of products, presumably containing **14h**, its *cis* diastereomer, and **15a** according to ^1H NMR and LCMS data (see Table 1 for the structures of the products). Heating of the crude product in AcOH led to the epimerization of the *cis* isomer to **14h**; however, the resulting ratio of **14h** and **15a** according to LCMS (**14h**/**15a** = 1:1.74) was less favorable than in the case of thermodynamically controlled conditions described above.

The ketimines **1k,l** were also evaluated in the reaction with anhydride **4** (Scheme 3). It was found that if the reaction was performed in xylene at 140 °C, the amides **15a,b** and the *N*-acylenamine **16** (isolated in the case of **1k**) were the major products formed;[13] no traces of the target compounds **14k,l** were observed. In $CHCl_3$ at rt, the compounds **15** and **16** were still the main products, but the tetrahydrobenzo[*d*]azepine derivatives **14k,l** were also isolated (21−24% yields). This is contrary to the previously reported results on reactions of ketimines with homophtalic anhydride, where the CCR products were formed in high yields upon heating in xylenes.[12a]

In our efforts for further modification of the products **14**, we studied esterification of the compounds **14e,i**. Surprisingly, the reaction of **14e** with *tert*-butyl alcohol, DCC, and DMAP in CH_2Cl_2 at 0 °C gave the *cis* esters **17e** (de 70%) instead of the expected *trans* isomers **18e**. Optimization of the reaction conditions showed that using Boc_2O−DMAP as a carboxylic group activator in CH_2Cl_2 at rt improved de of the product **17e** to 78%, whereas lowering the temperature to −5 °C gave the *cis* ester **17e** with 90% de and 84% yield (Scheme 4). Under the same conditions, **14i** was transformed to **17i** with even slightly better diastereoselectivity (94% de, 82% yield).

The relative configuration of the products **17e** and **17i** was confirmed by the values of $J(H^1-H^2)$ constants (1.3 and 0 Hz, respectively), which were considerably different from those observed in the *trans* series of the products **14a−i** (6.3−10.0 Hz) and apparently corresponded to $H^1-C^1-C^2-H^2$ torsion angles close to 90°.

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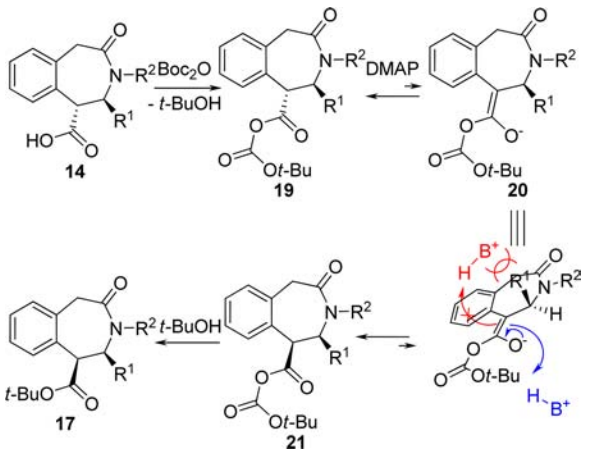
The formation of **17e,i** possibly included enolization of the activated intermediate **19** upon action of DMAP (Scheme 5).

Scheme 5



The protonation of the enolate **20** formed was sterically unfavorable from the *si* face; therefore, it occurred from the *re* face, which led to the formation of *cis* diastereomer **21**. The reaction of **21** with *tert*-butyl alcohol gave the final product **17**.

We found that epimerization of the product **17e,i** was possible upon action of a stronger base as compared to DMAP (DBU in MeOH). Under these conditions, an equilibration between **17e,i** and thermodynamically more stable **18e,i** was possible. The corresponding *trans* isomers **18e,i** were isolated in 81% yield and with 94–98% de. In this case, the $J(H^1–H^2)$ values were consistent with those observed in the *trans* series (10.3 and 6.6 Hz for **18e** and **18i**, respectively).

Since NOESY experiments with the esters **17** and **18** did not confirm unambiguously the configuration of these products, we performed deprotection of the *cis* esters **17e,i** (TFA, CH_2Cl_2, rt) (Scheme 5). The $J(H^1–H^2)$ values were close to 0 Hz for both products **22e,i**. Under analogous conditions, the starting carboxylic acids **14e,i** gave the products **23e** and **23i** with $J(H^1–H^2)$ = 9.9 and 10.2 Hz, respectively. These results confirm relative configuration of all the above-discussed esters and also demonstrate configurational stability of the *cis* isomers in the acidic media.

In conclusion, the evaluation of seven-membered cyclic anhydrides in a Castagnoli–Cushman reaction showed that adipic anhydride was much less reactive than its five or six-membered counterparts and did not lead to corresponding azepanes, whereas its benzo-annelated analogue allowed for the synthesis of 2,3-disubstituted 4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine-1-carboxylic acids with preparative yields (21–75%) and good *trans* diastereoselectivity. Unusual epimerization of these products was observed during synthesis of their *tert*-butyl esters, which opened access to diastereoselective synthesis of *cis* isomers.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03426.

Experimental details and copies of NMR spectra (PDF)
X-ray data for compound **14b** (CIF)

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Notes

The authors declare no competing financial interest.

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(11) Crystallographic data for **14b** have been deposited with the Cambridge Crystallographic Data Centre, 11 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk). Deposition No. 1513983.
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(13) It should be noted that the ratios of **15b** to **16** observed by LCMS might be affected by partial hydrolytic transformation of **16** to **15b** during the chromatography.

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