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The Castagnoli–Cushman reaction of bicyclic pyrrole dicarboxylic anhydrides bearing electron-withdrawing substituents

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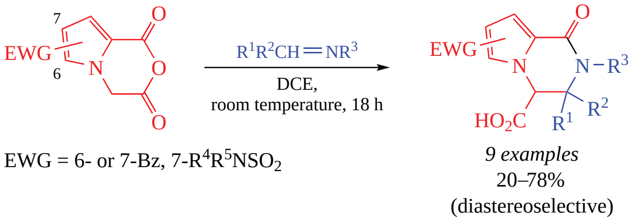
Four anhydrides of 1-(carboxymethyl)pyrrole-2-carboxylic acids bearing electron-withdrawing substituents at positions 6 or 7 of the bicyclic system have been investigated in the Castagnoli–Cushman reaction with imines. 6-Benzoyl- and 7-sulfamoyl-substituted anhydrides demonstrated lower reactivity while 7-benzoyl derivative displayed broader substrate scope. These findings have been rationalized from the mechanistic perspective.

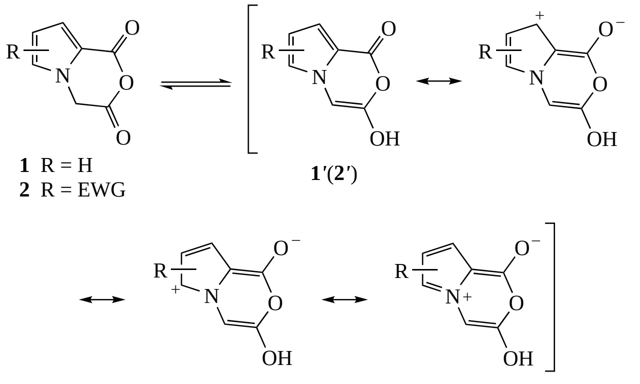


EWG = 6- or 7-Bz, 7-R^{4}R^{5}NSO$_2$

9 examples
20–78%
(diastereoselective)

Keywords: cyclic anhydrides, imines, Castagnoli–Cushman reaction, δ-lactams, enolization, resonance stabilization.

The cyclocondensation of α-C-H anhydrides of dicarboxylic acids with imines, known as the Castagnoli–Cushman reaction (CCR),[1,2] represents a facile and remarkably versatile way of constructing δ-, γ- and ε-lactams.[3–5] A particularly useful feature of this reaction, from the standpoint of chemical space exploration, is its ability to deliver lactam products based on different molecular scaffolds, depending on the type of cyclic anhydride employed.[6] Therefore, expanding the range of workable anhydrides[7] for the CCR is a worthy undertaking and, recently, has been a focal point of our research efforts. In particular, we have aimed at more 'enolizable' anhydrides which are known to be more reactive in the CCR.[8] Recently, we reported[9] an unusually reactive, pyrrole-fused anhydride **1** which reacted with a wide range of imines at ambient temperature (in contrast to glutaric anhydride which generally requires temperatures over 130 °C[10]). Tentatively, we attributed this high reactivity to the efficient resonance stabilization of the anhydride's enol form.[9] We subsequently reasoned that introduction of electron-withdrawing groups (EWG) at the pyrrole ring would lower the reactivity of the corresponding anhydrides **2** as it would destabilize the entire resonance hybrid of its enol form **2′** with positive charge delocalized in proximity to EWG (Figure 1). Herein, we report the results of testing this hypothesis.



1 R = H
2 R = EWG

1′(**2′**)

Figure 1 Pyrrole-fused anhydride **1** and its modified version **2** investigated in this work.

All pyrrole-fused cyclic anhydrides **2a–d** investigated in this work were obtained from a common precursor, methyl pyrrole-2-carboxylate (Scheme 1). Its regiodivergent AlCl$_3$- or ZnCl$_2$-promoted[11,12] Friedel–Crafts benzoylation followed by *N*-(methoxycarbonyl)methylation, hydrolysis of the diester and cyclodehydration gave 4- (**2a**) and 5-benzoyl (**2b**) anhydrides. Sulfochlorination afforded sulfonyl chloride **3** which was reacted with *p*-anisidine and morpholine. Sulfonamides thus obtained were subjected to the same final steps as in the syntheses of **2a**,**b** to give anhydrides **2c** and **2d** (see Scheme 1).

All of the four anhydrides **2a–d** thus synthesized were tested in the CCR with various imines **4** in DCE at room temperature (as described for **1**[9]). Much in line with our expectations, anhydride **2b** failed to give CCR products in yields of preparative value over 18 h. Prolonged reaction times or elevated temperature (up to reflux) did not improve the situation, which could be explained by the direct negative mesomeric destabilization of every charged resonance structure in the hybrid shown in Figure 1. The only case when the desired CCR product (**5e**) was obtained was in the reaction with highly reactive[9] *N*-ethyl imine **4a**. The other three anhydrides (**2a**,**c**,**d**) were successfully involved in the CCR with a markedly broader range of imines to give lactams **5a–d**,**f–i** (Scheme 2).[†] The diastereomeric ratios of isolated products did not differ from those determined from crude ^{1}H NMR spectra. The configuration of diastereomeric products was assigned based on $^3J_{H(3)H(4)}$ values being within 14–15 Hz and 4–5 Hz range for the *E*- and *Z*-isomers, respectively.

4-Benzoyl-substituted anhydride **2a** reacted with a much broader range of imine substrates compared to either **2b** or sulfamoyl-substituted counterparts **2c**,**d** (all three of the latter only reacted with *N*-alkyl imines). Although the reactivity of **2a** was noticeably

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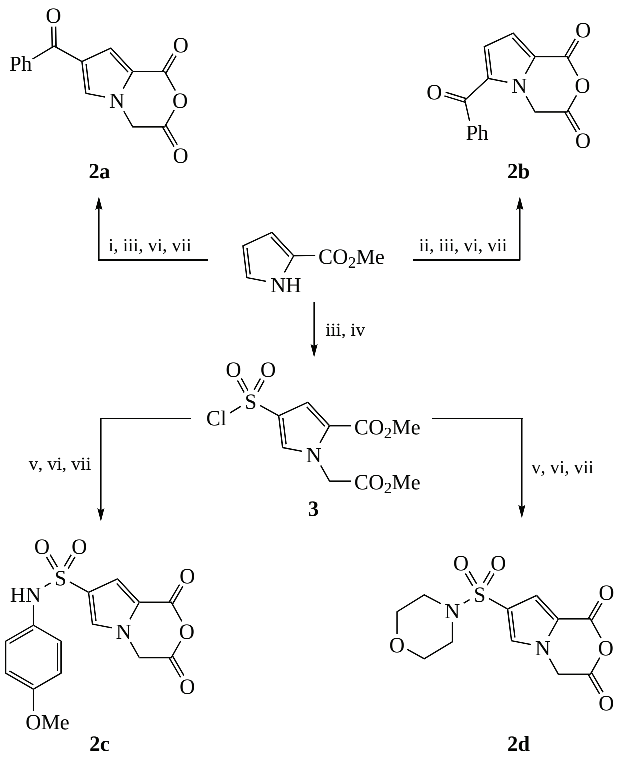
[†] *General procedure for the Castagnoli–Cushman reaction*. Anhydride **2** (0.2 mmol) was added to a solution of the imine (0.2 mmol) in DCE (0.3 ml), the mixture was stirred at room temperature for 18 h and concentrated *in vacuo*. The product was purified by HPLC; eluent: A) 0.1% TFA in water, B) 0.1% TFA in acetonitrile; gradient: 20% B (0–5 min), 20–90% B (5–40 min), 90–95% B (40–50 min). All products except **5c** and **5e** were isolated and characterized as mixtures of diastereomers.



Scheme 1 *Reagents and conditions*: i, PhCOCl, $AlCl_3$, DCE, 0→20 °C; ii, PhCOCl, $ZnCl_2$, DCE, 0→50 °C; iii, $BrCH_2CO_2Me$, NaH, DMF, 80 °C; iv, $ClSO_3H$, CH_2Cl_2, 20 °C, then $SOCl_2$; v, morpholine or *p*-anisidine, Et_3N, CH_2Cl_2, 0→20 °C; vi, aq. NaOH, THF, 20 °C; vii, $(CF_3CO)_2O$, EtOAc, 20 °C.

lower than that of **1**,[9] the involvement of α-C-H (**4c**,**d**) as well *N*-aryl imines (**4b**), *i.e.* substrates typically deemed problematic,[10] in the CCR with **2a** clearly speaks for its high reactivity. This is not particularly surprising since, on one hand, the benzoyl group in **2a** is not in direct conjugation with the positively charged atom in any of the resonance structures of this anhydride (in contrast to **2b**) and, on the other hand, sulfamoyl substituents possess stronger negative mesomeric effect which would destabilize the enol forms **2′c** and **2′d** and render these anhydrides less reactive with any imines except for *N*-alkyl ones.

In summary, we investigated four pyrrole-fused cyclic anhydrides bearing electron-withdrawing groups at either position 6 or 7 of the bicyclic system. Much in line with the expected correlation between anhydride reactivity in the Castagnoli–Cushman reaction and resonance stabilization of its reactive enol form, 6-benzoyl- and 7-sulfamoyl-substituted anhydrides possessed lower reactivity and gave the expected lactam adduct only with *N*-alkyl imines while 7-benzoyl derivative displayed broader substrate scope. These findings may provide helpful hints in the design of highly reactive cyclic anhydrides for the Castagnoli–Cushman reaction.

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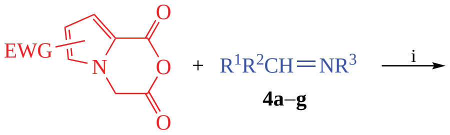
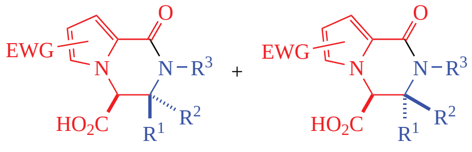
Online Supplementary Materials

Supplementary data associated with this article (procedures, analytical data and copies of ^1H NMR spectra) can be found in the online version at doi: 10.1016/j.mencom.2020.07.030.



2a–d **4a–g**

4a R^1 = H, R^2 = *p*-Tol, R^3 = Et
4b R^1 = H, R^2 = *p*-Tol, R^3 = 4-$MeOC_6H_4$
4c R^1 = H, R^2 = Et_2CH, R^3 = (2-furyl)methyl
4d R^1 + R^2 = $(CH_2)_5$, R^3 = Bu^i
4e R^1 = H, R^2 = Ph, R^3 = Me
4f R^1 = H, R^2 = 4-FC_6H_4, R^3 = 4-$MeOC_6H_4CH_2$
4g R^1 = H, R^2 = 4-$MeOC_6H_4$, R^3 = Bu



(*E*)-**5a**,**c**–**i** (*Z*)-**5a**–**i**

Reactants	Product	Yield (%)	*E*/*Z*
2a + **4a**	**5a**	74	6 : 1
2a + **4b**	**5b**	57	0 : 1
2a + **4c**	**5c**	51	5 : 1
2a + **4d**	**5d**	20	–
2b + **4a**	**5e**	42	9 : 1
2c + **4e**	**5f**	78	5 : 1
2c + **4f**	**5g**	67	7 : 1
2d + **4a**	**5h**	61	9 : 1
2d + **4g**	**5i**	69	9 : 1

Scheme 2 *Reagents and conditions*: i, anhydride **2** (0.2 mmol), imine (0.2 mmol), 1,2-dichloroethane (0.3 ml), room temperature, 18 h. For EWG specification, see Scheme 1.

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