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1,1′-Carbonyldiimidazole as a cyclodehydrating agent for the Castagnoli–Cushman reaction of dicarboxylic acids and imines

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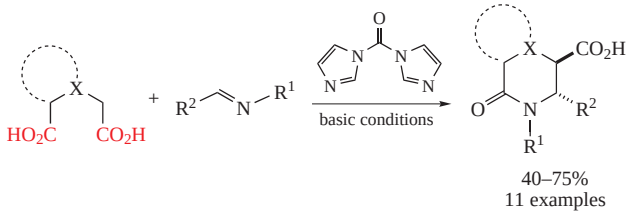
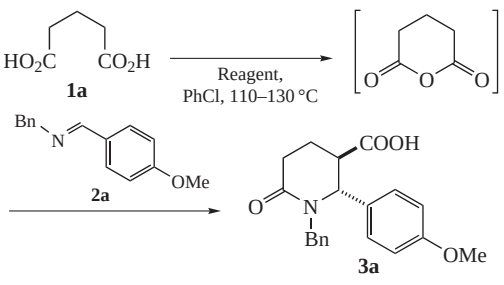
A novel protocol for the Castagnoli–Cushman reaction of dicarboxylic acids and imines comprises the use of 1,1′-carbonyldiimidazole as the cyclodehydrating agent to *in situ* produce the intermediate anhydrides. In contrast to previously developed procedure involving the use of acetic anhydride, the current protocol allows one to utilize substrates prone to acylation or acid-promoted transformations, which significantly broadens the reaction scope of lactams to be obtained.



The Castagnoli–Cushman reaction (CCR)[1,2] is a formal cycloaddition between cyclic α-CH anhydrides and imines giving facile access to a large variety of polysubstituted γ-, δ- and ε-lactams[3–5] often being biologically relevant scaffolds.[6,7] Most anhydrides are moisture-sensitive and commercially unavailable compounds in contrast to the corresponding dicarboxylic acids, therefore, the development of diacid-based protocols for the CCR is desired. Previously we reported[3] a protocol based on the use of acetic anhydride as the dehydrating agent. Despite many advantages offered by this procedure, its scope is limited to substrates which are immune to acylation and acid-promoted transformations. In this study, we aimed to find an alternative dehydrating reagent for CCR to overcome this limitation.

We started our investigation with the screening of other possible dehydrating agents, which could be used to generate anhydrides from dicarboxylic acids and which would be compatible with other CCR substrates, imines. The screening was performed for a model reaction of glutaric acid **1a** and imine **2a** conducted at 110 or 130 °C in chlorobenzene (Scheme 1, Table 1) in the presence of twelve different dehydrating agents. The chromatographic (HPLC) yield of the corresponding CCR product **3a** was monitored in each case to evaluate the efficiency of the reagent used. Only three of tested reagents provided considerable amounts of the target compound **3a** (see Table 1, entries 1–3), with 1,1′-carbonyldiimidazole (CDI) being the most effective one (54% HPLC and 40% isolated yield at 130 °C).

With the optimized reaction conditions in hand, we proceeded with exploring the scope of applicable substrates for the developed



Scheme 1

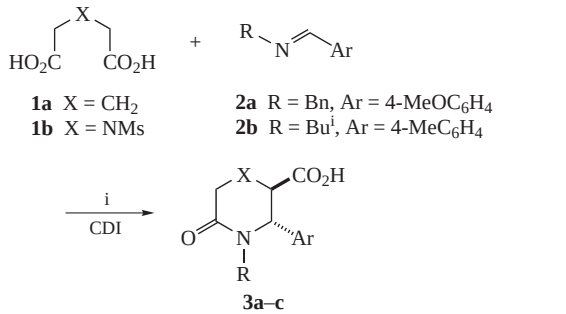
Table 1 Screening of cyclodehydrating agents in the CCR between compounds **1a** and **2a** (PhCl, 16 h).

Entry	Reagent	HPLC yield of **3a** (%)		Comparison reference[a]
		110 °C	130 °C	
1	Ac_2O	40	70	3
2	CDI	25	54	8
3	$(CF_3CO)_2O$	8	35	9
4	Oxalyl chloride	<5	31	10
5	$POCl_3$	<5	<5	11
6	$SOCl_2$	<5	<5	12
7	$B(OMe)_3$	<5	7	this work
8	AcCl	8	8	13
9	Boc_2O	10	<5	14
10	DCC	<5	<5	15
12	CCl_3CN	<5	<5	16
13	TsCl	<5	<5	17

[a] Reference for the anhydride synthesis from diacids.

protocol. Eleven five- and six-membered lactam products **3a–c**, **5a–c**, **7a–e** were obtained from five diverse carboxylic acids **1a**,**b**, **4a**,**b**, **6** and seven imines **2a–g** in good and high yields (40–75%) and with excellent *trans*-diastereoselectivity (except for compound **5c**) without any chromatographic separation (Schemes 2–4).[†] In case of homophthalic acid **6**, the reactions were performed at a significantly lower temperature (65 °C) since the corresponding

[†] *General procedure for the Castagnoli–Cushman reaction (Schemes 2–4).* 1,1′-Carbonyldiimidazole (1.1 mmol) was added in one portion to a stirred mixture of imine **2a–g** (0.9 mmol), dicarboxylic acid **1a**,**b**, **4a**,**b** or **6** (1 mmol) and dry solvent (1,2-dichloroethane or PhCl, 3 ml) (gas evolution!). The reaction mixture was heated at required temperature (65 or 130 °C) for 16 h in a sealed screw-cap vial. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and extracted with saturated sodium bicarbonate solution (5 ml). The aqueous layer was separated, and conc. HCl was added slowly at 0 °C to adjust pH to 1. After 1 h of standing at the same temperature, the precipitate formed was filtered, washed with water and crystallized from aqueous MeCN to afford pure compounds **3a–c**, **5a–c** or **7a–e**.

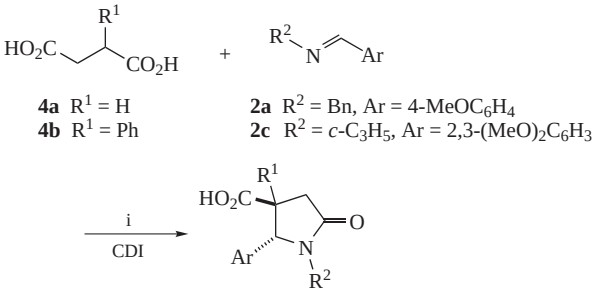


1a X = CH_2 **2a** R = Bn, Ar = 4-$MeOC_6H_4$
1b X = NMs **2b** R = Bu^i, Ar = 4-MeC_6H_4

3a–c

Reactants	Product	Yield (%)	*trans*/*cis*
1a + **2a**	**3a**	40	88 : 12
1a + **2b**	**3b**	60	> 20 : 1
1b + **2a**	**3c**	52	> 20 : 1

Scheme 2 *Reagents and conditions*: i, diacid (1 mmol), imine (0.9 mmol), CDI (1.1 mmol), PhCl (3 ml), 130 °C, 16 h.



4a R^1 = H **2a** R^2 = Bn, Ar = 4-$MeOC_6H_4$
4b R^1 = Ph **2c** R^2 = *c*-C_3H_5, Ar = 2,3-$(MeO)_2C_6H_3$

5a–c

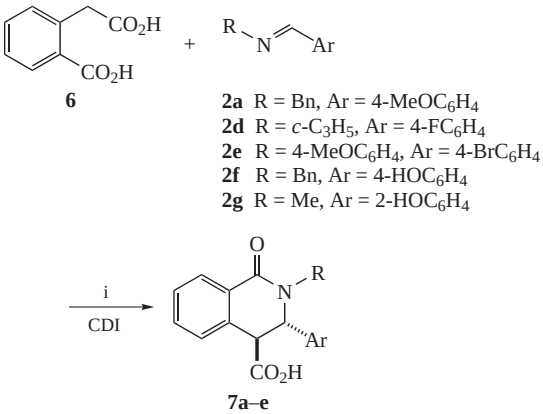
Reactants	Product	Yield (%)	*trans*/*cis*
4a + **2a**	**5a**	40	90 : 10
4a + **2c**	**5b**	52	> 20 : 1
4b + **2a**	**5c**	63	56 : 44

Scheme 3 *Reagents and conditions*: i, diacid (1 mmol), imine (0.9 mmol), CDI (1.1 mmol), PhCl (3 ml), 130 °C, 16 h.

anhydride possesses increased reactivity in the CCR. The relative configuration of products **3**, **5** and **7** was deduced from $^3J_{HH}$ values between methine protons from the lactam ring and their comparison with published NMR data for similar compounds.[18–20] Noteworthy, the reaction conditions were found suitable for substrates bearing acylation-prone OH group. In this way, the corresponding lactams **7d**,**e** were successfully prepared from homophthalic acid **6** and *para*- or *ortho*-hydroxyphenyl-substituted imines **2f**,**g** in 64 and 45% yields, respectively (see Scheme 4).

In conclusion, we have investigated the applicability of twelve different common dehydrating agents towards the Castagnoli–Cushamn reaction performed with dicarboxylic acids and imines. The best results were achieved with CDI, which afforded preparation of eleven diverse γ- and δ-lactams in 40–75% yields. In contrast to previously published procedure employing acetic anhydride as the cyclodehydrating agent, the developed protocol allows one to perform reactions under basic conditions and is compatible with nucleophilic moieties such as hydroxy groups.

*Representative example: (3*RS,*4*RS*)-2-cyclopropyl-3-(4-fluorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid* **7b**. Yield 243 mg (75%), white powder, mp 212.3–212.7 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.01 (br. s, 1H, COOH), 7.94 [d, 1H, CH(Ar), *J* 7.5 Hz], 7.40 [dt, 2H, 2CH(Ar), *J* 20.5, 7.3 Hz], 7.24 [d, 1H, CH(Ar), *J* 7.3 Hz], 7.16 [t, 2H, 2CH(Ar), *J* 7.1 Hz], 7.09 [t, 2H, 2CH(Ar), *J* 8.7 Hz], 5.30 (s, 1H, 3-CH), 4.16 (s, 1H, 4-CH), 2.85–2.72 (m, 1H, CH), 0.91 (p, 1H, *J* 6.8 Hz), 0.77 (q, 1H, *J* 7.7, 4.5 Hz), 0.72–0.53 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 172.3, 164.9, 161.7 (d, *J* 243.6 Hz), 136.4 (d, *J* 2.8 Hz), 133.8, 132.4, 130.2, 129.5, 128.4, 128.3 (d, *J* 8.3 Hz), 127.3, 115.9 (d, *J* 21.5 Hz), 61.3, 51.1, 30.2, 8.6, 5.7. HRMS (ESI), *m*/*z*: 326.1179 (calc. for $C_{19}H_{17}FNO_3$, *m*/*z*: 326.1187 [M + H]$^+$).



2a R = Bn, Ar = 4-$MeOC_6H_4$
2d R = *c*-C_3H_5, Ar = 4-FC_6H_4
2e R = 4-$MeOC_6H_4$, Ar = 4-BrC_6H_4
2f R = Bn, Ar = 4-HOC_6H_4
2g R = Me, Ar = 2-HOC_6H_4

7a–e

Reactants	Product	Yield (%)	*trans*/*cis*
6 + **2a**	**7a**	68	> 20 : 1
6 + **2d**	**7b**	75	> 20 : 1
6 + **2e**	**7c**	65	> 20 : 1
6 + **2f**	**7d**	64	> 20 : 1
6 + **2g**	**7e**	45	> 20 : 1

Scheme 4 *Reagents and conditions*: i, diacid (1 mmol), imine (0.9 mmol), CDI (1.1 mmol), 1,2-dichloroethane (3 ml), 65 °C, 16 h.

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Online Supplementary Materials

Supplementary data associated with this article (analytical data and copies of NMR spectra for compounds **3a–c**, **5a–c**, **7a–e**) can be found in the online version at doi: 10.1016/j.mencom.2019.05.016.

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