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New Heterocyclic Product Space for the Castagnoli–Cushman Three-Component Reaction

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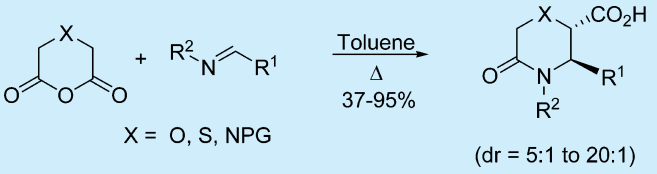
Supporting Information

ABSTRACT: Significant expansion of heterocyclic product space accessible by the Castagnoli–Cushman reaction (CCR) has been achieved via the use of glutaric anhydride analogues containing endocyclic substitutions with oxygen, nitrogen, and sulfur. Incorporation of these heteroatoms in the anhydride's backbone results in enhanced reactivity and generally lower temperatures that are required for the reactions to go to completion. These findings are particularly significant in light of the CCR recently recognized as an efficient tool for lead-oriented synthesis.

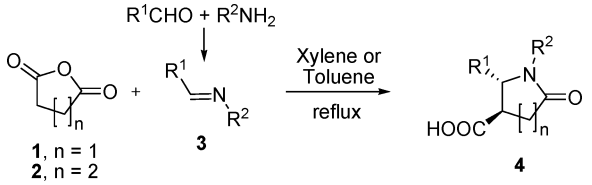


Reaction of alicyclic anhydrides (**1** and **2**) with imines **3** (either prepared in a separate step or formed in situ) provides convenient access to polysubstituted, predominantly transconfigured lactams **4** via a formal cycloaddition process at elevated temperatures (Scheme 1).[1] The reaction was first described by Castagnoli in 1969;[2] its scope and applications were thoroughly investigated in the work of Cushman (initially, in the Castagnoli lab).[3−6] The substrate scope of the reaction was subsequently expanded in the Cushman lab to include more reactive anhydrides such as homophthalic anhydride[7,8] and 3-phenylsuccinic anhydride,[9] which required lower (ambient) temperature for the reaction to proceed.

The usage of homopthalic anhydride is particularly notable as it provided a facile entry into the isoquinolonic acid core. This, in turn, gave rise to a fascinating medicinal chemistry program aimed at the discovery and optimization of novel tetracyclic topoisomerase I inhibitors based on indenoisoquinolone[10] and dibenzo[*c*,*h*][1,5]naphthyridinedione scaffolds.[11] Compounds belonging to the former series (LMP776 and LMP400) have advanced into human clinical trials for cancer,[12] and similar compounds have been implicated as chemopreventive agents in oncology.[13]

Due to the importance of this formal three-component reaction, which we term "the Castagnoli–Cushman reaction" (CCR), in medicinal chemistry and natural product synthesis,[1] further expanding its scope is a worthy undertaking, particularly with respect to the anhydride inputs. Unveiling of hetero-

Scheme 1. Reaction of Imines and Alicyclic Anhydrides



Scheme 2. CCR of Succinic Anhydrides Containing Exocyclic Heteroatom Substituents[15]

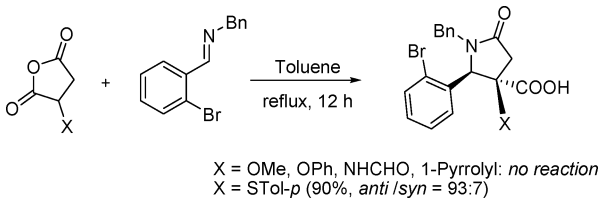
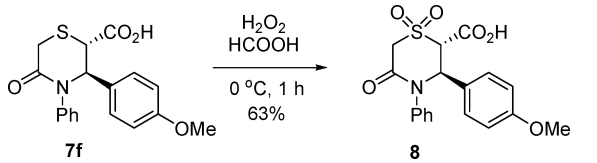


Table 1. Screening of Reaction Conditions toward 7a[a]

solvent	35 °C (24 h)	60 °C (4 h)	80 °C (2 h)	110 °C (2 h)
1,4-dioxane	16%	35%	43%	ND
toluene	24%	52%	65%	52%
ethyl acetate	24%	46%	35%	ND
acetonitrile	17%	15%	ND	ND
THF	13%	ND	ND	ND
chloroform	1.5%	ND	ND	ND

[a]Data represent NMR yield of the product (*trans* + *cis*) determined relative to *n*-tetradecane as internal standard (see Supporting Information); ND, not determined.

Scheme 3. Preparation of Sulfone Lactam 8



aromatic analogues of homophthalic anhydride[14] represented a significant step forward. Recent work by Shaw included in situ

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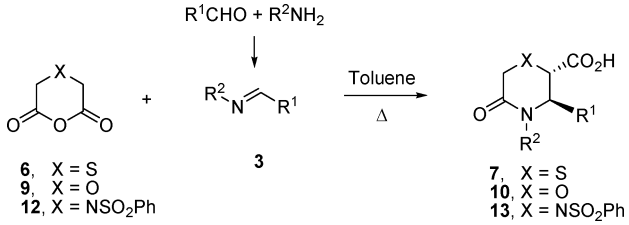
Table 2. 5-Oxothiomorpholine-, 5-Oxomorpholine-, and 5-Oxopiperazine-2-carboxylic Acids (7, 10, and 13) Obtained via the CCR of Respective Anhydrides (6, 9, and 12)



entry		X[a]	R^1	R^2	time	dr[b]	isolated yield, %[c]
1	**7a**	S	4-$MeOC_6H_4$	Bn	2 h[d]	5:1	61 (7:1)
2	**7b**	S	4-FC_6H_4	4-$ClC_6H_4CH_2$	3 h[e]	6:1	54 (trans)[f]
3	**7c**	S			2 h[d]	5:1	77 (5:1) 57 (*trans*)
4	**7d**[g]	S	4-$O_2NC_6H_4$	*n*-Bu	6 h[e]	8:1	57 (11:1)
5	**7e**	S	4-MeC_6H_4	4-$MeOC_6H_4$	6 h[e]	9:1	84 (9:1) 68 (19:1)
6	**7f**	S	4-$MeOC_6H_4$	Ph	2 h[d]	10:1	71 (10:1)
7	**7g**	S	4-MeC_6H_4	4-ClC_6H_4	6 h[e]	14:1	73 (*trans*)
8	**7h**[g]	S	CO_2Et	4-$MeOC_6H_4$	5 h[e]	7:1	37 (*trans*)
9	**10a**	O	4-$MeOC_6H_4$	Bn	4 h	10:1	79 (11:1)
10	**10b**	O	4-MeC_6H_4	Et	4 h	10:1	71 (*trans*)
11	**10c**	O	4-FC_6H_4	4-$ClC_6H_4CH_2$	17 h	>15:1	33 (*trans*)
12	**10d**	O	3,4-$(MeO)_2C_6H_3$	*n*-Bu	5 h	>10:1	70 (*trans*)
13	**10e**	O	4-$MeOC_6H_4$	Me	5 h	5:1	79 (5:1)
14	**10f**	O	4-FC_6H_4	*n*-Pr	8 h	>10:1	60 (*trans*)
15	**10g**	O	4-$MeOC_6H_4$	*t*-Bu	4.5h	>20:1	76 (trans)[f]
16	**10h**	O			19 h	10:1	66 (*trans*)
17	**13a**	NSO_2Ph	4-$MeOC_6H_4$	Bn	2 h	9:1	80 (8:1)[f]
18	**13b**	NSO_2Ph	2-$MeOC_6H_4$	Bn	1 h	5:1	80 (8:1) 63 (*trans*)
19	**13c**	NSO_2Ph	4-MeC_6H_4	4-ClC_6H_4	1.5 h	17:1	94 (17:1) 55 (*trans*)
20	**13d**	NSO_2Ph	COOEt	4-$MeOC_6H_4$	2.5 h	7:1	37 (*trans*)
21	**13e**	NSO_2Ph	4-MeC_6H_4	4-$MeOC_6H_4$	1.5 h	9:1	89 (9:1) 68 (*trans*)
22	**13f**	NSO_2Ph	3,4-$(MeO)_2C_6H_3$	*n*-Bu	1.5 h	6:1	64 (8:1)
23	**13g**	NSO_2Ph		*n*-Pr	1.5 h	20:1	86 (20:1) 63 (*trans*)
24	**13h**	NSO_2Ph			2 h	9:1	78 (12:1) 55 (*trans*)
25	**13i**	NSO_2Ph	4-$MeOC_6H_4$	Ph	1 h	10:1	84 (10:1) 51 (*trans*)[f]
26	**13j**	NSO_2Ph	4-$MeOC_6H_4$	*t*-Bu	1 h	11:1	78 (*trans*)

[a]Reactions with **9** (X = O) and **12** (X = NSO_2Ph) were run at 110 °C. [b]Diastereomeric ratio (*trans/cis*) in reaction mixture (determined by crude ^1H NMR). [c]The dr of isolated products is given in parentheses. [d]Reaction conducted at 80 °C. [e]Reaction conducted at 110 °C. [f]Confirmed by single-crystal X-ray analysis (see Supporting Information). [g]CCR product was converted to the methyl ester prior to isolation (see Supporting Information).

generation of 3-substituted succinic anhydride by reacting a thiol with maleic anhydride and not only enabled a true multicomponent format for this reaction and facilitated the reaction but also allowed manipulation of the stereochemistry and increased skeletal complexity of the final products.[15−18] Surprisingly, succinic anhydrides containing exocyclic oxygen and nitrogen substituents had been found to be ineffective (Scheme 2).[15]

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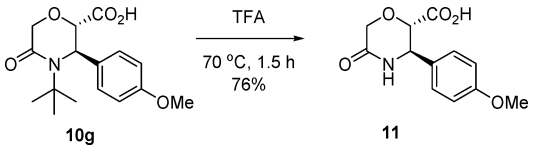
Scheme 4. *tert*-Butyl Group Removal from Lactam 10g



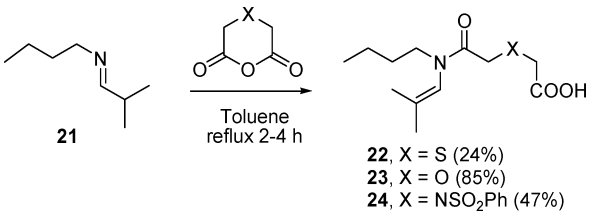
Similar examples reported by Shaw include the use of sulfone-[19] and cyano-substituted[20] succinic anhydrides. However, no examples of heteroatom-containing cyclic anhydrides had been reported at the time we initiated this study.[21] Such an extension of the reaction scope would be particularly desired, in light of the recently demonstrated[22,23] propensity of the CCR to deliver lead-like compounds. Herein, we fill this void and report our recent results obtained using oxa, aza, and thia analogues of glutaric anhydride in the Castagnoli–Cushman reaction.

Prompted by the findings from the Shaw group,[15] we first investigated the CCR of thiodiglycolic anhydride (**6**), which was conveniently prepared on multigram scale using a modified literature protocol.[24] To our delight, it reacted in toluene, rapidly and cleanly, with imines **3** to furnish 5-oxothiomorpholin-2-carboxylic acid products **7a–h**. The temperature required to complete the reaction was markedly lower compared to that of the CCR of unsubstituted glutaric anhydride, which is consistent with the expected influence of the sulfur atom on the α-CH acidity of the anhydride and the resulting facilitation of the overall CCR.[15] The yields obtained were good to excellent, in addition to the satisfactory diastereoselectivity. We also screened several other solvents and temperature regimens in preparation of **7a** as a model reaction. This confirmed toluene at 80–110 °C to be the optimal conditions for thiodiglycolic anhydride (Table 1).

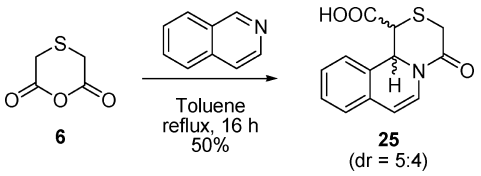
Compounds **7a–h** contain a divalent sulfur atom, which introduces a metabolic liability from a drug design prospective.[25] Sulfone or sulfoxide analogues of **6** are unknown, but compounds **7** can be oxidized to the respective sulfones, as was demonstrated by preparation of compound **8** (Scheme 3). The latter represents an intriguing polyfunctional building block, the synthetic potential of which remains to be unveiled.

Encouraged by these initial findings (and also by the new literature data[21]), we proceeded to investigate the applicability of diglycolic anhydride, **9**, in the CCR. With this reagent, the reactions with imines **3** were found to be high yielding and displayed clear preference for the transconfigured products **10a–h** (Table 2). The reactions proceeded to completion within 4–19 h in refluxing toluene, with the conditions being much less forceful than those reported by Burdzhiev.[21]

Scheme 6. *N*-Acyl Enamine Formation from Imine 21



Scheme 7. Isoquinoline in the CCR with 6

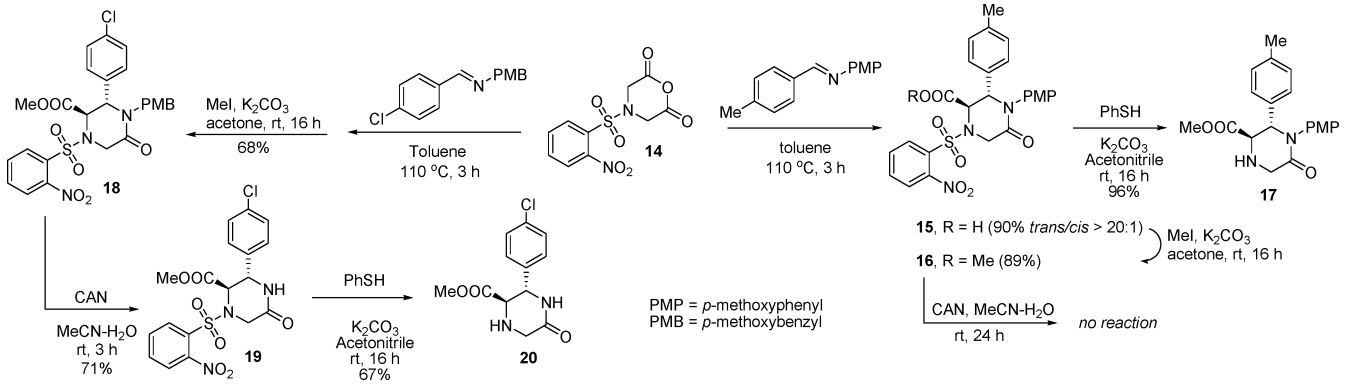


Product **10g** provides a notable (and rare[9]) example of incorporating a hindered amine into the CCR product structure. It can also be easily converted into lactam **11** on treatment with TFA (Scheme 4).

Having explored the CCR for the thia and oxa analogues of glutaric anhydride, we were curious to see if a similar endocyclic placement of a nitrogen atom within the structure of glutaric anhydride (as in **12**) would deliver an effective anhydride partner for the CCR (cf. the respective exocyclic substitution of succinic anhydride with formylamino group, which completely disabled the subsequent reaction with an imine partner, Scheme 2). Reaction with **12** was complete within 1–2.5 h in refluxing toluene and delivered the expected lactams **13a–j** in good to excellent yields, with a significant preference for the *trans*-isomer (Table 2). Compounds **13** represent a substantial advancement in terms of structural diversity of heterocycles that are accessible by the CCR. They contain the privileged piperazine core[26] and an α-amino acid motif and may be of interest for peptidomimetic design[27] and drug lead optimization.[28]

This mandated orthogonal protection of the piperazinone scaffold. The initial attempt to introduce the acid-labile Boc group at N^1 in combination with a PMP group at N^4 (which could be removed later under oxidative conditions, e.g., on treatment with CAN[29]) was unsuccessful because Boc-protected morpholin-2,6-dione (prepared as described in the literature[30]), surprisingly, failed to furnish a CCR product.

Scheme 5. Protecting Group Manipulation on the Piperazin-2-one Scaffold



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Our next choice of protecting group was (*o*-nitrophenyl)-sulfonyl (ONPS) present in **14** (see Supporting Information for preparation). The respective CCR product **15** was converted into methyl ester **16** and then into **17** via a facile ONPS removal. However, the PMP group was found to be resistant to removal with CAN and had to be replaced with PMB in **18**. The latter was conveniently and orthogonally deprotected to give **19** and **20** in sequential fashion (Scheme 5).

With the exception of a few modestly yielding reactions,[1] aromatic (or non-enolizable aliphatic) aldehydes are commonplace carbonyl components used in the CCR. With enolizable aldehydes, the anhydride component acts primarily as an acylating agent and the reaction exclusively yields *N*-acyl enamines. We also observed the formation of such compounds (**22**−**24**) in the reaction of imine **21** with thia, oxa, and aza analogues of glutaric anhydride (Scheme 6).

The use of cyclic imines (such as dihydroisoquinoline) in the CCR is quite common[7,31] but was found to be poorly workable for the anhydrides studied here. To our surprise, however, thiadiglycolic anhydride (but not its oxygen- and nitrogen-containing counterparts) reacted with isoquinoline to give tricyclic compound **25**, with modest yield and diastereoselectivity (Scheme 7). To our knowledge, this is the first example of unsubstituted isoquinoline taking part in the CCR.

In conclusion, the successful employment of heteroatom-containing analogues of glutaric anhydride in the CCR described in this paper significantly broadens the heterocyclic product space accessible by this reaction. This is likely to result in the development of new focused libraries for drug discovery. Such efforts are underway in our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02014.

Experimental procedures and characterization data for compounds **6**, **7a**−**h**, **8**, **9**, **10a**−**h**, **11**, **12**, **13a**−**j**, **14**−**20**, and **22**−**25**. Crystal data and full crystallographic information for compounds **7b**, **10g**, and **13a,i** (PDF)

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Notes

The authors declare no competing financial interest.

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