Catalysis

Divergent Synthesis of γ-Amino Acid and γ-Lactam Derivatives from *meso*-Glutaric Anhydrides

Simon N. Smith, Ryan Craig, and Stephen J. Connon*[a]

Abstract: The first divergent synthesis of both γ-amino acid and γ-lactam derivatives from *meso*-glutaric anhydrides is described. The organocatalytic desymmetrisation with $TMSN_3$ relies on controlled generation of a nucleophilic ammonium azide species mediated by a polystyrene-bound base to promote efficient silylazidation. After Curtius rearrangement of the acyl azide intermediate to access the corresponding isocyanate, hydrolysis/alcoholysis provided uniformly high yields of γ-amino acids and their *N*-protected counterparts. The same intermediates were shown to undergo an unprecedented decarboxylation–cyclisation cascade in situ to provide synthetically useful yields of γ-lactam derivatives without using any further activating agents. Mechanistic insights invoke the intermediacy of an unconventional γ-*N*-carboxyanhydride (γ-NCA) in the latter process. Among the examples prepared using this transformation are 8 APIs/molecules of considerable medicinal interest.

γ-Aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the brain.[1] Decreases in levels of endogenous GABA play a pivotal role in the pathophysiology of many psychiatric and neurological disorders including: anxiety, depression, Parkinson's and Alzheimer's disease, stress and neuropathic pain.[2] This often necessitates pharmacological intervention in the form of more bioavailable, 3-substituted derivatives of GABA (Figure 1 A) such as the former "blockbuster" drug pregabalin (**1**),[3] the homologous gabapentinoids (i.e. **2**–**6**)[4] and GABOB (**7**)[5] to ameliorate symptoms. The wider presence of the GABA *motif* in organic chemistry and in living systems is mirrored by the prevalence of the corresponding cyclised γ-lactam derivatives (Figure 1 B). These structures are found widely in active pharmaceutical ingredients (APIs, for example, '*racetams*' **8**–**9**)[6] and other bioactive compounds (e.g. rolipram (**10**)),[7] but are also core scaffolds in a variety of natural products such as the imidazole alkaloids **11** and **12**.[8]

Despite several chemical[9] and chemoenzymatic[10] methods being available for the enantioselective synthesis of 3-substituted GABA analogues, often the lowest cost routes to γ-amino acid APIs involve classical resolution of a racemate.[3a,11] Traditional, metal-free synthetic strategies rely either on the hydrolysis of the corresponding γ-lactam (which itself is non-trivial to access),[12] or require generation of a γ-nitroester (or related equivalent) via Michael-type chemistry.[3a,13] The latter can often be challenging in the case of β,β-disubstituted Michael acceptors, and the resulting Michael adducts must be further transformed to attain the target structure by either: *i*) hydrolysis/decarboxylation of acyl anion equivalent followed by Ni-catalysed reduction of the nitroalkane or *ii*) reductive cyclisation of the γ-nitroester followed by γ-lactam hydrolysis. Although methods exist for the synthesis of 3-substituted γ-amino acids from cyclic anhydrides by Schmidt, Hoffman, Lossen and similar reactions,[3a,13,14] these routes are multi-step and require the use of harsh reagents with poor functional group compatibility. We postulated that the difficulties associated with *rapidly and efficiently* generating γ-amino acids could

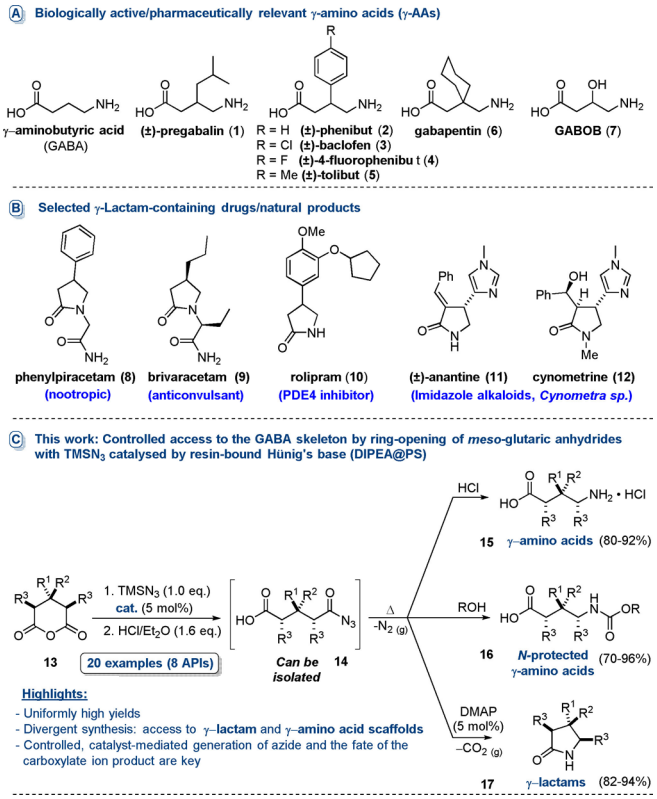

Figure 1. Biologically/pharmaceutically important γ-amino acids, γ-lactams and the addition of azide to *meso*-anhydrides.

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https://doi.org/10.1002/chem.202003280.

be obviated if γ-carboxyacyl azides could be catalytically accessed via the desymmetrisation of *meso*-glutaric anhydrides followed by a Curtius rearrangement in situ.

Reports examining the reactivity of azide towards cyclic anhydrides are sparse. Seminal work in 1966[15] described the treatment of phthalic anhydride derivatives with azide, albeit under forcing conditions (i.e. DMF/DMSO, >150 °C, excess NaN_3), yielding benzimidazolones. The reaction mechanism was purported to proceed via a cyclic intermediate β-*N*-carboxyanhydride (β-NCA, or *'Leuchs anhydride'*).[16,17] More recently, NCAs have been investigated in the context of drug delivery systems,[18] due to their capacity to form polypeptides on treatment with a variety of basic or nucleophilic initiators.[19] Consequently, a smaller subset of NCA literature broaches the synthetic challenges of accessing aliphatic β-NCAs while avoiding polymerisation by the treatment of succinic anhydride derivatives with an excess of $TMSN_3$.[19a,20] However a general, catalytic solution to this problem has proven elusive.

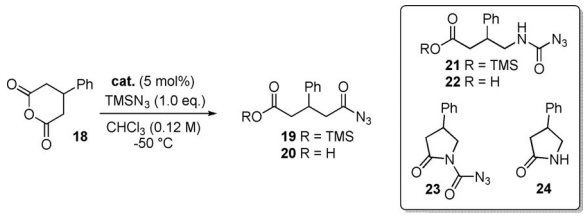
Herein, we report the first smooth catalytic desymmetrative addition of $TMSN_3$ to *meso*-glutaric anhydrides **13** to generate **14** after protonolysis (Figure 1C). Intermediate **14** is remarkably versatile: it can either be isolated, or, after removal of a heterogeneous catalyst by filtration (and without purification) transformed into either γ-amino acids **15** or their *N*-protected carbamate derivates **16**. The hemi-acyl azide **14** can also—without the requirement for any activating agents—be converted to synthetically-desirable γ-lactams **17** in the presence of a nucleophilic catalyst (Figure 1C).

We began investigations by examining the reactivity of $TMSN_3$ (**Caution**: see the Supporting Information Section 2.3.1.) towards 3-phenylglutaric anhydride (**18**) at room temperature; intending to access amino acids and carbamates through intermediate silylazidation of product **19** in a range of solvents (Table 1, entries 1–5). Although thermal decomposition at room temperature of acyl azide **19** was expected to yield the corresponding isocyanate to some degree by Curtius rearrangement,[21] we were surprised to instead observe an array of isocyanate-derived products **21**–**24**. Carbamoyl azide formation from isocyanates has been known to occur only under treatment with HN_3 promoted by strong acids at elevated temperatures,[22] and has not been observed in cases where succinic anhydrides were used. In this case, carbamoyl azide formation is attributed to fast trapping of the intermediate isocyanate by a second equivalent of $TMSN_3$ to form **21**. This process was found to occur less readily in toluene (entry 1) and chlorinated solvents (entries 2 and 3) compared to either of THF (entry 4) or acetonitrile (97% yield of **21**, entry 5). Furthermore, we were initially surprised to observe concurrent formation of lactams **23** and **24** in chlorinated solvents (vide infra).

Although further manipulations of carbamoyl azides are known to provide either *N*-protected or free amines,[22c,23] both derivatisations would require the extrusion of volatile, explosive and toxic hydrazoic acid (HN_3). In the interest of safety and synthetic utility, we pursued an alternative route utilising equimolar $TMSN_3$. Reduction of the reaction temperature to circumvent thermal Curtius rearrangement provided **19** cleanly, albeit with poor conversion (6%, entry 6). Attempts at Brønsted acid catalysis of the silylazidation process lead to inhibition relative to the uncatalysed reaction (entry 7) while Lewis bases such as $Ph_3P{=}O$ and DMF were identified as weak promoters (entries 8 and 9, respectively). DMAP was found to catalyse the reaction to a significant extent (entry 10) and conventional poorly-nucleophilic tertiary amines were subsequently examined in an effort to partition nucleophilic- from base catalysis (entries 11 and 12). Although every subsequent amine evaluated behaved as an effective promoter (entries 12–13), weakly Brønsted-basic pyridine was demonstrated to be the most efficient homogeneous catalyst system (entry 14). Substitution of pyridine for polystyrene-bound Hünig's base (DIPEA@PS, entry 15) and raising the reaction temperature from −50 °C to −20 °C (entry 16) not only shortened the reaction times significantly, but provided a facile means to remove the catalyst from the reaction after completion via filtration.

Mechanistic investigations into the ring-opening process (see the Supporting Information) supported the formation of an ammonium azide, in situ-derived from the Brønsted basic amine precatalyst and HN_3 ($pK_a = 4.72$) present in commercial supplies of $TMSN_3$ which is produced in small amounts by hydrolysis with adventitious H_2O. Anhydride **18** can undergo nu-

Table 1. Catalyst screening and optimisation of experimental conditions.



Entry[a]	Catalyst	Solvent	*t* [h]	Yield **19** [%][b]
1[c]	–	PhMe	72	0
2[d]	–	$CHCl_3$	72	0
3[e]	–	CH_2Cl_2	72	0
4[f]	–	THF	72	0
5[g]	–	MeCN	96	0
6	–	$CHCl_3$	24	6
7	AcOH	$CHCl_3$	24	0
8	$Ph_3P{=}O$	$CHCl_3$	24	5
9	DMF	$CHCl_3$	24	14
10	DMAP	$CHCl_3$	16	63
11	proton sponge	$CHCl_3$	16	76
12	DIPEA	$CHCl_3$	6	97
13[h]	DABCO	$CHCl_3$	16	82
14	pyridine	$CHCl_3$	6	>98
15	DIPEA@PS	$CHCl_3$	3	97
16[i]	DIPEA@PS	$CHCl_3$	1.5	>98

[a] The reactions summarised in entries 1–5 were performed at room temperature. [b] Determined by ^1H NMR spectroscopic analysis using 4-iodoanisole as an internal standard. [c] Carbamoyl azide **21** (28%) observed. [d] Lactams **23** (28%) and **24** (4%) observed. [e] Lactams **23** (18%) and **24** (4%) recovered after chromatography. [f] Complex reaction mixture. [g] Clean conversion to carbamoyl azide **21** (48%). The use of 2 equivalents $TMSN_3$ facilitated the isolation of **22** in 97% yield upon desilylation of **21** with MeOH (10.0 equiv.). [h] Reaction time to complete conversion <10 min with 5 mol% AcOH as co-catalyst (86%). [i] Reaction temperature −20 °C.

cleophilic ring-opening by this active azide species to generate a kinetically-stable ammonium carboxylate. This intermediate is silylated by $TMSN_3$ to complete the catalytic cycle and liberate the acyl azide product **19**. The process thereby obviates any hazards associated with stoichiometric generation of HN_3.

It was found that after protodesilylation of **19** with ethereal HCl and evaporation of the reaction mixture, hemi-acyl azide **20** is recovered as a crystalline solid; the sole by-product produced in the reaction is volatile TMSCl. This acyl azide could—after considerable experimentation—undergo clean Curtius rearrangement to produce the corresponding isocyanate, which was susceptible to hydrolysis in THF with concentrated aqueous HCl to provide the corresponding amino acid derivative.

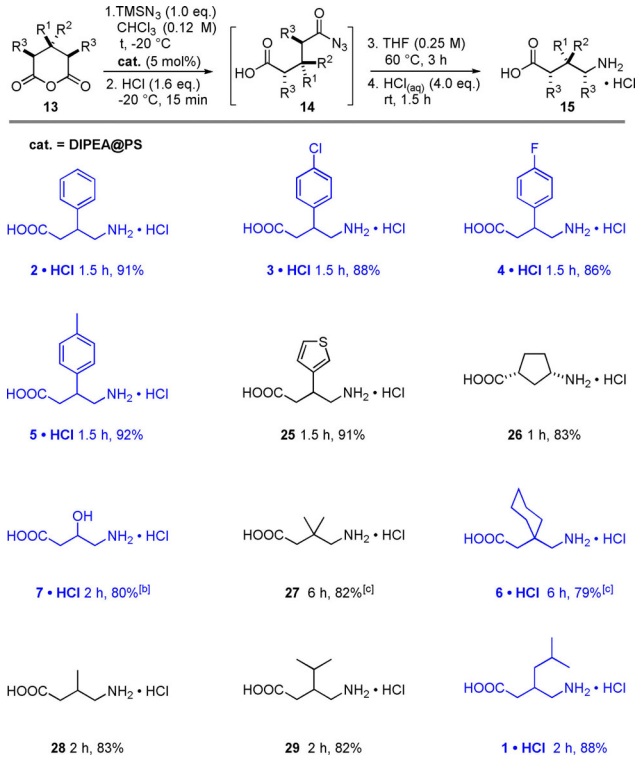
With conditions for efficient γ-amino acid synthesis in hand, attention was turned to the question of substrate scope (Table 2). Nucleophilic azidation of a range of substituted glutaric anhydrides of general type **13** in the presence of polystyrene-supported Hünig's base (at 5 mol% loading) and stoichiometric loadings of $TMSN_3$ followed by the addition of ethereal HCl generated hemi-acyl azides **14**; which could be filtered to remove the catalyst and subjected (without purification) to a Curtius rearrangement followed by acidic hydrolysis to afford γ-amino acid hydrochloride salts **15**. Using this procedure, (±)-phenibut, (±)-baclofen, (±)-fluoribut and (±)-tolibut hydrochlorides were prepared in very good-to-excellent yields (i.e. **2**–**5**, respectively). The heterocyclic thiophene bioisostere analogue **25** could be synthesised with comparable efficiency. Bicyclic glutaric anhydrides were also found to be suitable substrates, undergoing reaction with to provide exclusively the 1,3-*cis*-amino acid **26** in good yield and without epimerisation, which is a key intermediate in the synthesis of carbocyclic nucleosides.[24] Aliphatic, 3-substituted anhydrides required marginally extended reaction times relative to their aryl homologues, but nonetheless provided good-to-excellent yields of six further aliphatic amino acids, most notably three clinically-relevant compounds as their hydrochloride salts: 3,3-disubstituted gabapentin (**6**, 79% yield), (±)-GABOB (**7**, 80% yield) and (±)-pregabalin (**1**, 88% yield).

In a further demonstration of the versatility of these synthetic intermediates, isocyanate **31** (formed quantitatively from anhydride **30**) could be trapped by alcohols in situ to provide orthogonally-protected GABOB carbamates (Fmoc, CBz, Alloc) in good-to-excellent yields that correspond approximately to the nucleophilicity of the primary alcohol (Scheme 1, **32**–**34**).

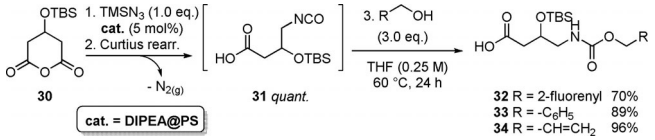
Although γ-isocyanato acid **31** was found to be stable in solution for short periods of time at room temperature (ca. 2–3 h), over extended intervals in $CDCl_3$, or if attempts were made to isolate neat samples of **31**, rapid decomposition was observed. This degradation was accompanied by an unanticipated decarboxylative-lactamisation providing variable yields of the corresponding γ-lactam; a similar process to that observed during our preliminary investigations (vide supra). The mechanism by which the lactamisation proceeded was not immediately apparent.

Under identical conditions to those previously described, hemi-acyl azides **14** were generated from **13** (Table 3). After removal of volatiles and replacement of the solvent with anhydrous $CHCl_3$, thermal Curtius rearrangement yielded isocyanates **35** cleanly. After screening potential catalytic systems to

Table 2. Nucleophilic azidation of *meso*-glutaric anhydrides: substrate scope.[a]

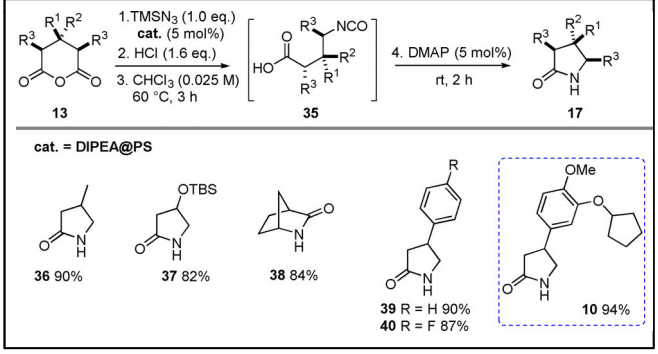


[a] Isolated yield. [b] From 3-*O*-TBS protected derivative. [c] Reaction concentration 0.25 M. Compounds highlighted in blue are known GABAergic pharmaceuticals.



Scheme 1. Synthesis of *N*-Fmoc, CBz and Alloc GABOB carbamates.

Table 3. Ring-contractive lactamisation of *meso*-glutaric anhydrides via organocatalytic desymmetrisation with $TMSN_3$.



promote subsequent lactamisation (see the Supporting Information), it was found that high-dilution conditions in conjunction with the use DMAP at 5 mol% loading were essential to prevent oligomerisation. Accordingly, a representative sample of five γ-lactams were prepared in up to 90% yield from their corresponding *meso*-anhydrides (Table 3, **36**–**40**), and PDE4 inhibitor **10** in 94% isolated yield.

With respect to mechanistic detail, the literature lends some insight. The reaction between a carboxylic acid and an isocyanate to produce amides has its roots in the late 19th century, and involves the formation of a "mixed carboxylic-carbamic anhydride" (i.e. an acyclic NCA) as an intermediate.[25] Similar to the lactamisation, this process involves an extrusion of CO_2 by an unknown mechanism,[26] which has been shown through isotopic labelling experiments to originate from the *sp*-carbon of the isocyanate.[27] Furthermore, two unrelated articles involving polymerisation provide significant evidence for the formation of a 7-membered NCA (**40**).[19b,28] Based on these observations and significant parallels in our own investigations, we propose the mechanism of the DMAP-catalysed lactamisation proceeds through a γ-NCA in analogous fashion by a Steiglich-type acyl-transfer (Figure 2). Isocyanate **35** undergoes nucleophilic attack by DMAP forming an electrophilic *N*-carbamoylpyridinium carboxylate **35a** after proton-transfer. This species is capable (at high dilution) of intramolecular cyclisation via **35b**, forming γ-NCA **40** which enters the next catalytic cycle. The NCA is attacked at the more electrophilic acyl centre by DMAP to give tetrahedral intermediate **41**, which then decomposes to yield an *N*-acylpyridinium carbamate salt **42**. This species collapses to release cyclic **17** by decarboxylation and regenerate the catalyst.

In summary, a new divergent synthetic strategy to access substituted γ-amino acids and γ-lactams from *meso*-glutaric anhydrides has been developed. The silylazidation was found to proceed most efficiently under heterogeneous catalysis promoted by polystyrene-bound Hünig's base via a nucleophilic ammonium azide species formed in situ. The resulting acyl azide was used directly as a metastable precursor to access a unique isocyanate intermediate by thermal Curtius rearrangement. The synthetic utility of these isocyanates was demonstrated by either hydrolysis in situ to provide the corresponding γ-amino acid salt (up to 92% yield), or alcoholysis to yield the *N*-protected derivatives (up to 96% yield) and their cyclisation without the aid of any activating agent to the corresponding γ-lactams (up to 94% yield), the latter process proceeding through an unusual γ-NCA intermediate. Among the examples prepared using this transformation are 8 APIs/molecules of considerable medicinal interest. Studies to further explore the scope and utility of this process are underway.

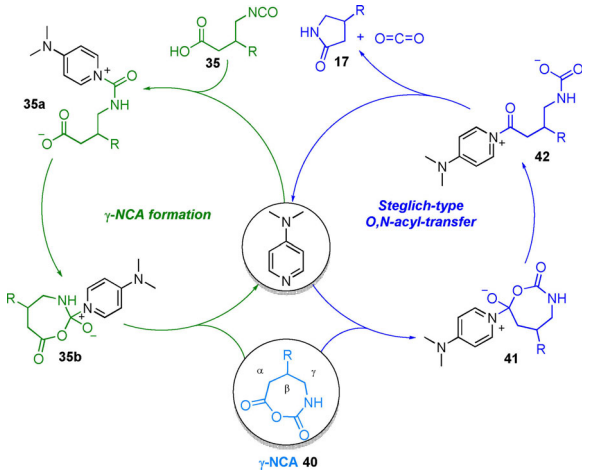


Figure 2. Proposed general catalytic cycle.

Acknowledgements

This publication has emanated from research conducted with the financial support of the Irish Research Council (GOIPG/2017/972) and the Synthesis and Solid State Pharmaceutical Centre (SSPC), funded by Science Foundation Ireland (SFI, 12\RC\2275) and the European Regional Development Fund (EDRF).

Conflict of interest

The authors declare no conflict of interest.

Keywords: azides · desymmetrisation · *meso*-anhydride · γ-amino acids · γ-lactams

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Manuscript received: July 13, 2020
Accepted manuscript online: ■■ ▮▮, 0000
Version of record online: ■■ ▮▮, 0000

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doi.org/10.1002/chem.202003280
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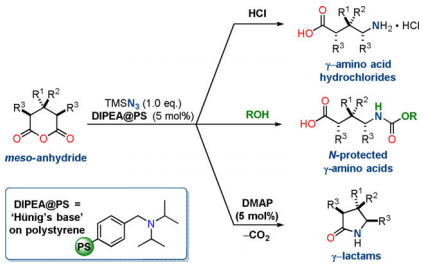

Desymmetrisation: A divergent synthetic strategy to access both γ-amino acid and γ-lactam derivatives by treatment of *meso*-glutaric anhydrides with $TMSN_3$ is reported (see scheme).