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Twisting the ethano-Tröger's base: the bisamide†

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The typically planar amide when incorporated into bicyclic systems can undergo a significant distortion from planarity resulting in physical properties and reactivity that deviate from classical amide behaviour. Herein, we report a succinct protocol that utilises potassium permanganate to selectively α-oxygenate the benzylic position of ethano-Tröger's base derivatives to yield a new class of twisted bisamides. Additionally, we report the first synthesis of an ethano-Tröger's base derivative bearing substituents in the positions *ortho* to the nitrogen atoms.

Introduction

The amide group, ubiquitous in biology and chemistry, favours planarity as a direct consequence of resonance stabilization.[1] However, from a reactivity point of view, the more exotic amides are those that exhibit deviation from planarity and are seen in certain peptides,[2] as well as small organic molecules.[3] The twist angle $\tau = (\omega_{C4-C3-N-C2} + \omega_{O-C3-N-C1})/2$ describes the deviation from co-planarity between the carbonyl π-orbital and the nitrogen lone pair (Fig. 1).[4] It varies between the values that describe a planar geometry (τ = 0°, 180°), wherein most amides lie, and those that represent a highly distorted geometry (τ = 90°).[5]

The twisting of the amide-bond is normally accompanied by an energy penalty, which can be ascribed to the pyramidalisation of the nitrogen, which causes the attenuation of the $n_N-\pi^*_{C=O}$ resonance reaching a minimum in the case of τ = 90°. This high-energy geometry may be construed as the transition state of *E*/*Z* isomerisation of amides,[7] and only a few examples are known to be stable in this state.[5,8] Due to their implications in uncharacteristic amide reactivity,[5a,9] and applications in biology and medicinal chemistry,[8,10] twisted amides represent an area in chemistry that has attracted the attention of organic chemists[11] and accordingly several strategies have been developed to synthesise them. These are broadly classified as: (a) steric repulsion due to the substituents on the nitrogen,[3b–f,12] (b) conformational effects,[13] (c) electronic effects, wherein the amide-nitrogen bears electron-withdrawing groups,[14] and (d) steric restriction due to being confined in rings.[5,15] An overwhelming majority of twisted-amide molecules known in the literature incorporate a single amide moiety.[11] In 2012, Wärnmark and co-workers showed that potassium permanganate can be used to oxidize the benzylic C–H bonds of Tröger's base (TB) (Fig. 2), 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine[16] (**4**), to yield a twisted bisamide 2,8-dimethyl-6*H*,12*H*-5,11-methanodibenzo[*b*,*f*][1,5]diazocine-6,12-dione (**2**) in 28% yield.[15a] As part of our research on Tröger's base,[17] we developed a route for the chemo- and stereoselective oxygenation and nitrogenation of the ethanodibenzodiazocine core of ethano-Tröger's base (ETB) (Fig. 2), 2,8-dimethyl-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine[18] (**5**), using a combination of palladium acetate, *N*-bromosuccinimide and potassium acetate.[19]

In this report, we present the synthesis and characterisation of twisted bisamides derived from an ETB scaffold.

Results and discussion

Here we would like to report an extension of Wärnmark's protocol,[15a] which utilizes potassium permanganate to chemoselectively oxidize the benzylic carbons of **5a**, leaving the bridge carbons untouched to yield **6a**. Optimisation of the reaction conditions revealed that the original setup was the best (Table 1, entry 1 *vs.* entries 2–6), and that nine equivalents of $KMnO_4$ and the phase transfer catalyst were required. The quality of methylene chloride used had no effect on the reaction at all. Furthermore, we could also run the reaction effectively in acetonitrile at 50 °C using nine equivalents of $KMnO_4$ (Table 1, entry 9 *vs.* entries 7–8 and 10). Toluene, however, was not a suitable solvent for this transformation (Table 1, entry 11).

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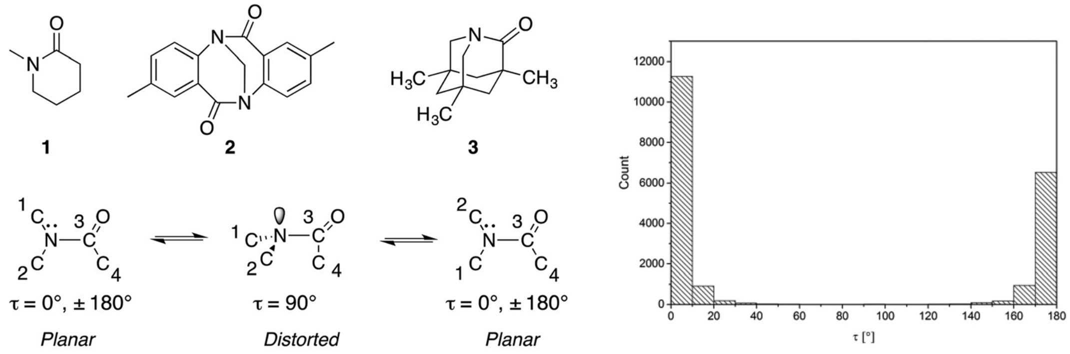


$$\tau = \frac{\omega_{C4\text{-}C3\text{-}N\text{-}C2} + \omega_{O\text{-}C3\text{-}N\text{-}C1}}{2}$$

Fig. 1 Top left: Planar amide **1**, and distorted amides **2** and **3**. Bottom left: Planar and distorted geometries of amides. Right: Twist-angle distribution of tertiary amides in the Cambridge Structural Database (CSD)[6] on 8th December 2015. Data for 13 000 structures.

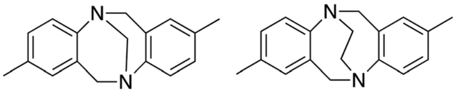
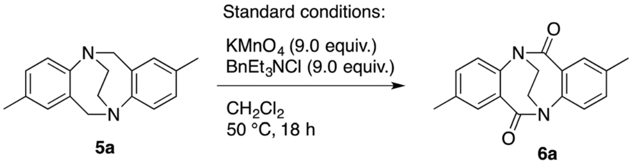


Fig. 2 Tröger's base **4**, and ethano-Tröger's base **5**.

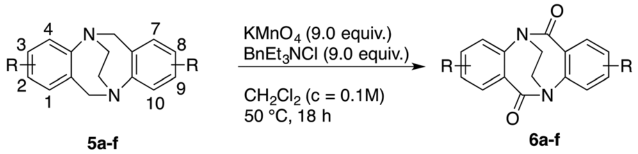
Table 1 Exploring the reaction conditions



Entry	Deviation from standard conditions	Ratio **6a** : **5a**[a]	**6a**[b] [%]
1	—	90 : 10	48
2	0.0 equiv. of $KMnO_4$	0 : 100	—
3	0.0 equiv. of $BnEt_3NCl$	0 : 100	—
4	3.0 equiv. of $KMnO_4$	10 : 90	ND
5	6.0 equiv. of $KMnO_4$	45 : 55	ND
6	9.0 equiv. of $KMnO_4$ at 25 °C	0 : 100	—
7	3.0 equiv. of $KMnO_4$ in CH_3CN at 50 °C	30 : 70	ND
8	6.0 equiv. of $KMnO_4$ in CH_3CN at 50 °C	57 : 43	ND
9	9.0 equiv. of $KMnO_4$ in CH_3CN at 50 °C	86 : 14	46
10	9.0 equiv. of $KMnO_4$ in CH_3CN at 25 °C	03 : 97	ND
11	Toluene	0 : 100	—

[a] Ratio determined by ^{1}H NMR. [b] Isolated yield after flash column chromatography. ND = not determined.

Table 2 Scope of the benzylic oxidation of **5** to bisamide **6**



Entry	Starting material	R	Product	Yield[a] [%]
1	**5a**	2,8-Me	**6a**	48
2	**5b**	2,8-OMe	**6b**	52
3	**5c**	2,8-Br	**6c**	42
4	**5d**	2,8-Cl	**6d**	30
5	**5e**	2,8-COOEt	**6e**	0
6	**5f**[b]	2,8-Me, 4,10-F	**6f**	0

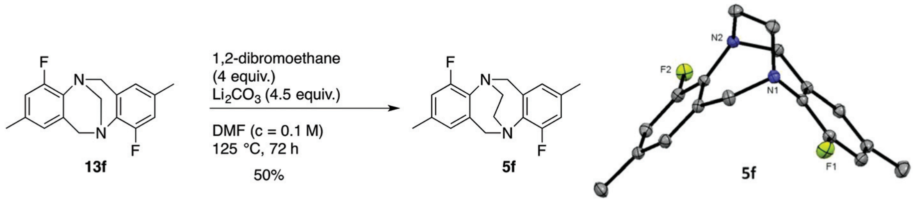
[a] Isolated yield after flash column chromatography. [b] 4,10-Difluoro-2,8-dimethyl-6*H*,12*H*-5,11-ethanodibenzo[*b*,*f*][1,5]diazocine was used.

Using the optimised conditions, we have successfully subjected different 2,8-disubstituted ETB derivatives to this transformation (Table 2, entries 1–4). Electron-donating groups on the aromatic rings increase the reactivity of the system (Table 2, entries 1 and 2) whereas electron-withdrawing groups inhibit the reaction (Table 2, entries 3–5).

Compound **5f** is the first example of an ETB analogue bearing substituents *ortho* to the nitrogen atoms. This compound was synthesized *via* a modified bridge replacement procedure[18] wherein **13f** was stirred with 1,2-dibromoethane and Li_2CO_3 in DMF at 125 °C for 72 h to afford **5f** in 50% yield (Scheme 1). To our disappointment **5f** did not react with potassium permanganate (Table 2, entry 6), suggesting that the electron withdrawing effect of the fluorine substituents hampers the reaction, which is consistent with the reduced yield when bromide, chloride or ester functionalities are present on the aromatic rings (Table 2, entries 3–5).

The bisamide products **6a–6d** are poorly soluble in most organic solvents; only methylene chloride and pyridine were able to dissolve them to a fair extent. Nevertheless the separation of the products from the starting material is straightforward and the products belong to the rare class of medium-bridge lactams.[11a]

With bisamides **6a–6d** in hand, we initiated a detailed study of their structure and reactivity. To our delight, we were



Scheme 1 Synthesis of ETB analogue **5f**. Displacement ellipsoid plot is drawn at 50% probability. Hydrogen atoms are omitted for clarity.

able to grow crystals of **6a** and **6d** that were of suitable quality for single-crystal X-ray diffraction analysis (Fig. 3).

The twist angles (τ) of bisamides **6a**, **6d** and monoamide **7a** (*vide infra*) indicate a significant divergence from planarity. The carbonyl groups are planar whilst the nitrogens are in between planar and tetrahedral. Relevant structural and spectroscopic parameters are compared in Table 3 with those of 1-methyl-2-piperidone **1** (τ = 2.5°), Tröger's base derived amide **2** (τ = −43.7°) and 1-aza-2-adamantan-one **3** (τ = 90.5°).

The ETB derivatives **6a** and **6d** show C(O)–N and C═O bond lengths that are substantially longer and shorter respectively than those of 1-methyl-2-piperidone (**1**), a planar amide, but not as anomalous as in Kirby's most twisted amide, 1-aza-2-adamantanone, **3**. Twisted amides are known to exhibit abnormal infrared profiles wherein the wave numbers of the $\nu_{C=O}$ absorptions increase with an increase in τ.[3d] **6a** and **6d** show IR absorption values which are in between those of **1** and **2**. The ^{13}C NMR chemical shifts for the carbonyl carbon resonance are also susceptible to variations, although to a minor extent.[3d] Interestingly, the δ $^{13}C_{C=O}$ values (179.1 ppm for **6a**, 176.8 ppm for **6d** and 181.1 ppm for **7a**) are higher than those reported for Wärnmark's twisted amide

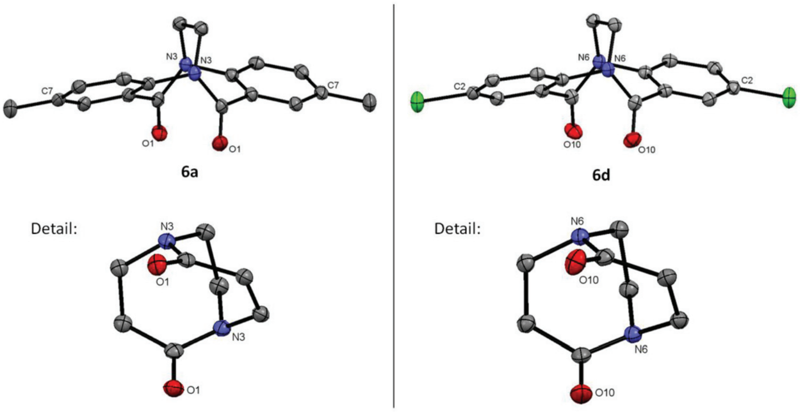
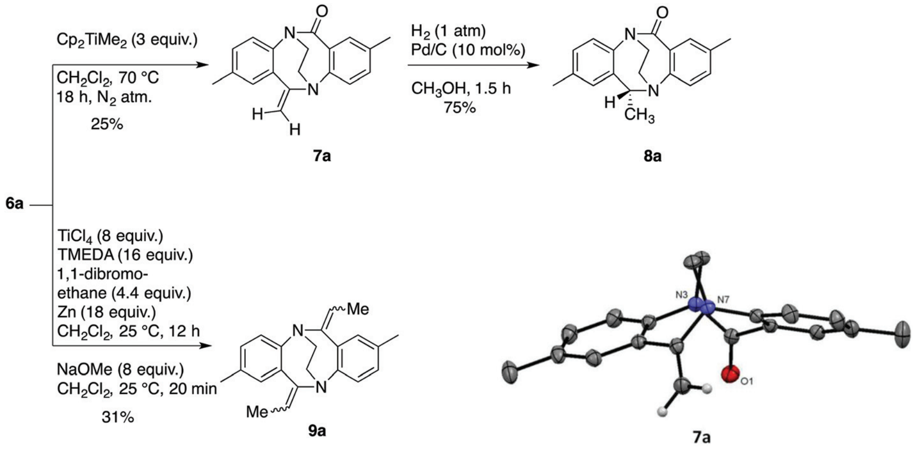


Fig. 3 Solid state structures of **6a** and **6d**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms are omitted for clarity.

Table 3 Selected structural and spectroscopic parameters of products **6a**, **6d** and **7a** and comparison with relevant literature examples

	1 [20]	**6a**	**6d**	**7a**	**2** [14 a]	**3** [5 a]
τ (°)	2.5	29.8(1)	−28.1(2)	30.3(2)	−43.7	90.5
Sum of bond angles at N (°)	358.9	344.5(2)	344.4(2)	346.3(2)	333.0	325.7
Sum of bond angles at C═O (°)	359.9	359.9(2)	359.8(2)	359.8(2)	359.8	359.9
Bond length C(O)–N (Å)	1.352	1.402(2)	1.399(2)	1.386(2)	1.437	1.475
Bond length C═O (Å)	1.233	1.215(2)	1.215(2)	1.224(2)	1.209	1.195
Distance O–O (Å)[a]	na	3.529(1)	3.425(2)	3.957(2)[b]	5.34	na
Distance N–N (Å)[c]	na	2.668(2)	2.666(2)	2.700(2)	2.39	na
Angle between aromatic rings Ψ (°)	na	138.1(1)	140.1(1)	143.3(1)	120.1	na
C_2–C_8 distance (Å)[d]	na	8.4	8.4	8.4	7.8	na
IR $\nu_{C=O}$ (cm^{-1})	1653	1674	1666	1667	1694	1732
^{13}C NMR C═O (δ, ppm) ($CDCl_3$)	165.0	179.1	176.5	181.3	170.1	200.0

[a] O–O distance measured between the two amide-oxygen atoms. [b] In **7a** O–O distance is replaced by the O–C distance between the amide-oxygen atom and the terminal carbon of the double bond. [c] N–N distance measured between the two nitrogen atoms of the ring. [d] C_2–C_8 distance is defined as the distance between the aromatic carbons which were *para* to the nitrogen atoms in the parent aniline precursor.

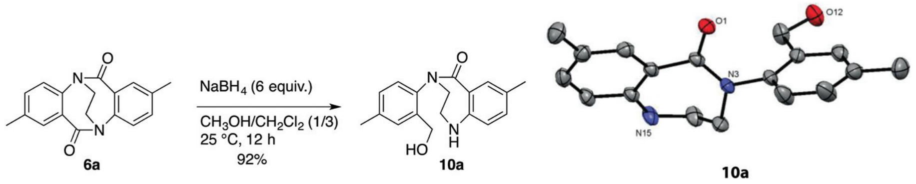


Scheme 2 Investigation of the reactivity of the carbonyl bonds in **6a**. Top: Reaction of **6a** with the Petasis reagent, [Cp$_2$TiMe$_2$], to enamine **7a** and further reduction to **8a**. Displacement ellipsoid plot is drawn at 50% probability. Hydrogen atoms are omitted for clarity. Bottom: Bis-olefination of **6a** to give bis-enamine **9a**.

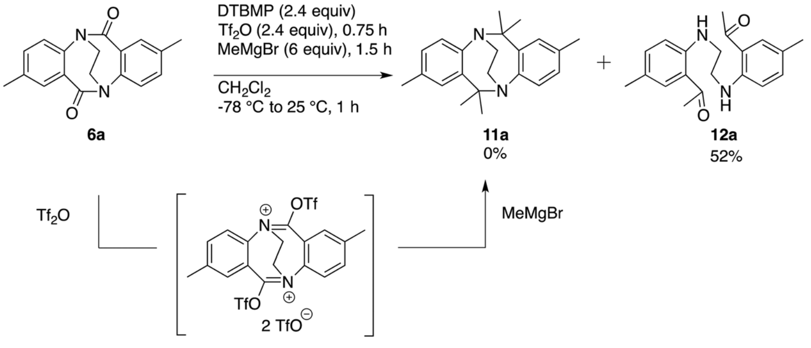
(**2**; 170.1 ppm) wherein τ is greater at −43.7°. Furthermore, **6a**, **6d** and mono-amide **7a** (*vide infra*) have the shallowest cavities and the longest C$_2$–C$_8$ distances of all known ETB and TB analogues.[15a,19]

We next turned our attention to probe the reactivity of the amide moiety in **6a**; more specifically we wanted to ascertain whether the amide was sufficiently twisted to exhibit the amino-ketone behaviour that is associated with twisted amides.[5a] We initially attempted the Wittig-olefination; unfortunately, **6a** did not react with either (ethoxycarbonylmethylene)-triphenylphosphorane or methyltriphenylphosphonium bromide even at elevated temperatures and we only recovered the starting material in quantitative yield. Lawesson's reagent also did not react with either of the carbonyl groups. At this point we decided to use the more oxophilic titanium-based reagents to functionalize the amide, and to our delight the Petasis reagent, [Cp$_2$TiMe$_2$], led to the olefination of one of the carbonyl bonds to yield enamine **7a**, which was selectively reduced to **8a** (Scheme 2, top).

In an attempt to reduce the second amide group, we initially subjected **7a** to the reaction with [Cp$_2$TiMe$_2$]. However, this did not yield the desired product. We then attempted to



Scheme 3 Reduction of **6a** with NaBH$_4$ to give ring-opened mono-amide **10a**. Displacement ellipsoid plot is drawn at 50% probability. Hydrogen atoms are omitted for clarity.



Scheme 4 1,2-Addition of methylmagnesium bromide to **6a**. DTMB = 2,6-di-*tert*-butyl-4-methylpyridine.

olefinate **6a** under Takai's conditions[21] and we were able to obtain the bis-olefinated product **9a** (Scheme 2, bottom), which was found to be rather unstable and rapidly degraded. At this point, we suspected that the close proximity of the two amide-oxygen atoms (3.5 Å *vs.* 5.3 Å seen in **2** where the Wittig-olefination had shown good results) might be responsible for the molecule's inert behavior. We therefore thought it prudent to explore the reactivity of twisted amide **6a** with smaller nucleophiles. The attempted reduction of the amide with $LiAlH_4$ in a mixture of pyridine/THF (2 : 1) afforded no product;[22] the starting material was recovered exclusively. Surprisingly, the reaction of $NaBH_4$ with **6a** in a mixture of methanol and methylene chloride yielded a product that at first seemed to contain one amide and one hemi-aminal moiety. However, X-ray crystallographic analysis revealed that the diazocine ring had been cleaved during the reaction. The subsequent *in situ* reduction of the aldehyde yielded **10a** (Scheme 3).

Next, we treated **6a** with trifluoromethanesulfonic anhydride (Tf_2O) in an attempt to generate a transient anti-Bredt iminium,[23] which would be alkylated with methylmagnesium bromide to deliver the α-alkylated ETB species **11a**.[24] However, instead we observed the formation of 1,2-addition product **12a** in 52% isolated yield (Scheme 4). Similar results were obtained in the absence of DTMB and Tf_2O suggesting the Grignard reagent added directly to the carbonyl carbon.

Conclusion

In conclusion, we have utilised $KMnO_4$ as an oxidant for the selective α-oxygenation of ETB derivatives. Importantly, these conditions are selective for oxidation of the benzylic positions and are complementary to our previously described method in which only the alkyl bridge is functionalised. X-ray diffraction analysis revealed **6a** and **6d** to be examples of the relatively rare class of twisted bisamides. In addition, they have the shallowest cavities of all TB and ETB analogues investigated to date. We have carried out a reactivity study on this kind of twisted amide and shown that they possess a smaller range of reactivity as compared to the Tröger's base derivative **2**. In addition, we have synthesised the first *ortho*-substituted ethylene-bridged Tröger's base derivative **5f**.

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