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Convenient Preparations of 2,4-Methanopyrrolidine and 5-Carboxy-2,4-methanopyrrolidines

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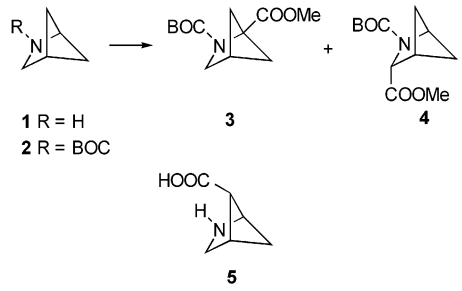
Abstract: An efficient four-step synthesis of *N*-BOC-5-*syn*- and 5-*anti*-carboxymethanopyrrolidines (**12** and **13**) and the conversion of **12** to *N*-BOC-methanopyrrolidine (**2**) are described.

Because pyrrolidines are important components of many biologically significant molecules,[1] there have been numerous efforts to prepare conformationally constrained pyrrolidines that might mimic naturally occurring structures as well as provide insights into substrate−receptor interactions of bioactive molecules.[2] Bridged methanopyrrolidines **1** are one such type of rigid structure.[3] We recently described a five-step synthesis from pyridine of *N*-BOC-methanopyrrolidine **2** and showed how it can be used to prepare *N*-protected esters of both the naturally occurring 2,4-methanoproline **3** and also 3,5-methanoproline **4**.[4,5] Both isomers are useful in the study of conformational effects on protein stability.[6] An isomeric 5-*syn*-carboxy-2,4-methanopyrrolidine **5** has been prepared by Huet and co-workers in 18 steps from 1,2-dichloroethylene and maleic anhydride.[3a] Acid **5** has potential use in the field of peptidomimetics as a β-isomer replacement for proline in peptides. We desired a more efficient route to these and related structures that would reduce the number of chromatography steps that have plagued previous syntheses.



Tamura,[7] Schell,[8] Swindell,[9] and Winkler[10] have shown that irradiation of appropriately substituted *N*-allyl-*N*-vinyl amides provides access to the 2-azabicyclo[2.1.1]-hexane ring system. Using these precedents, we have developed efficient syntheses of *syn*-5-carboxymethanopyrrolidine **12** and methanopyrrolidine **2** and also have made available the novel *anti*-5-carboxymethanopyrrolidine **13**.

As part of our first attempt to prepare a derivative of the acid **5**, we made the photo substrate **6** in 60% yield

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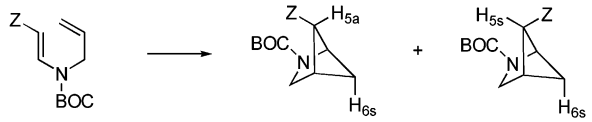
by addition of allylamine to methyl propiolate and subsequent reaction with di-*tert*-butyl carbonate in the presence of DMAP.[10] The trans stereochemistry could be assigned to **6** on the basis of a doublet (J = 13.1 Hz) for a vinyl hydrogen assigned adjacent to nitrogen at δ 8.20. Unfortunately, photoirradiation of **6** in acetonitrile (1−24 h, 0.01 M, argon) did not provide the desired esters **8** or **9**.



6 Z = COOMe
7 Z = COMe

8 Z = COOMe
10 Z = COMe
12 Z = COOH

9 Z = COOMe
11 Z = COMe
13 Z = COOH

We next envisioned the synthesis of acids **12** or **13** by oxidative cleavage of ketones **10** or **11**. Although stereochemical details were not reported, irradiation of a dienone **7**, prepared in three steps from commercially available materials in 74% overall yield, was reported by Kwak and Winkler.[10] The outcome was ketone **10** or **11** or a mixture of both. In a reinvestigation of this reaction the precursor *N*-BOC-enamide **7** was prepared as described with only chromatography of the final product. The trans geometry is assigned to **7** on the basis of a 14.6-Hz coupling constant for the vicinal hydrogens of the enamide double bond. Over nine separate trials, photoirradiation of **7** afforded mixtures of a major syn-ketone **10** (71−91% by ^{1}H NMR) and a minor anti-ketone **11** (9−29%). Isolation resulted in an increased percentage of the major isomer **10** (82−97% of isolated ketone) indicative of some loss of the minor isomer **11** upon silica gel chromatography. The 5-*syn*-acetyl stereochemistry for **10** is assigned by the absence of long-range coupling between H_{5a} at δ 2.64 and H_{6s}. Additionally, H_1 at δ 4.58 shows the expected small coupling J = 1.5 Hz with H_{5a}. In the *anti*-acetyl isomer **11** H_{5s} at δ 2.70 is a doublet (J = 8.0 Hz) coupled to H_{6s}.[4] The syn orientation of the acetyl and nitrogen functionalities in the major isomer **10** following the irradiation process requires a reversal of the anti stereochemistry of these groups found in the precursor olefin **7**.[11] While surprising, the result is not unprecedented.[12]

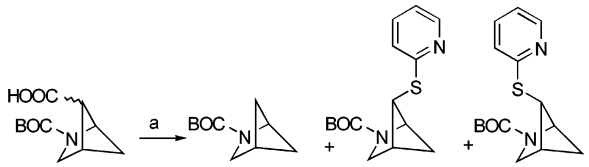
There was some concern prior to attempting the oxidation of ketones **10** and **11** since it is known that these and similar ketones ring open in the presence of refluxing alcohol or base.[7a,8,9] Nevertheless, it is possible to oxidize syn-ketone **10** by using aqueous sodium hypochlorite in THF for 1 h at 35 °C to afford acid **12** (95%).[13] The 5-syn stereochemistry could be assigned to **12** on the basis of the doublet appearance for H_{6s} at δ 1.34 (J = 8.0 Hz), as expected in the absence of long-range W-coupling with H_{5a} at δ 2.8 (br).[14] Acid **12** with trimethylsilyldiazomethane afforded ester **8**.[15] Similarly, anti-ketone **11** could be oxidized to give the first reported example of a 5-anti acid **13** as evidenced by the doublet for H_{5s} at δ 2.65. Esterification of acid **13** afforded ester **9**; esters **8** and **9** are clearly absent in the irradiation of diene ester **6**.

TABLE 1. Decarboxylation of Acid 12[a]

entry	reagent	conditions	product(s)	yield (%)[b]
1	*t*-BuSH	light[c,d]	**2**	48−65
2	Bu_3SnH	light[c,e]	**2**	42
3	Bu_3SnH	heat[f]	**2**	48
4	TTMSS	light[g,h]	**2**	51
5	TTMSS	light[g,i]	**2** + **14** + **15**	31 + 4 + 11

[a] The Barton ester, prepared from acid **12** and 2-mercaptopyridine *N*-oxide, was reacted with the indicated reagent. See ref 16. [b] Isolated. [c] 400-W tungsten lamp, AIBN. [d] Benzene, 3 h. [e] DMF, 30 min. [f] Benzene, 3 h. [g] 600-W tungsten lamp, AIBN. [h] THF, 1.5 h. [i] Cyclohexane, reflux, 30 min.

The methanopyrrolidine **2** was prepared from the purified acid **12** (Table 1). Decarboxylations in which the Barton ester from **12** is reacted with *tert*-butyl thiol give good yields of **2** and the product is easy to purify, but there is a potential odor problem (entry 1).[16] Tin reagents give slightly lower yields (entries 2−3). Tris(trimethylsilyl)silane (TTMSS) as reductant gave a moderate yield of **2** in THF (entry 4), while the interesting thioethers **14** and **15** were isolated in minor amounts if the reaction was carried out in cyclohexane (entry 5).[17] The stereochemistry of the 5-*anti*-thiopyridyl isomer **14** could readily be assigned on the basis of the doublet (J = 8.1 Hz) for the H_{5s} proton at δ 3.61 coupled to H_{6s} at δ 1.58 (t, J = 8.1 Hz). This long-range coupling is absent for H_{5a} at δ 4.13 (sbr) in the 5-*syn*-thiopyridyl isomer **15**.



12 + **13** **2** **14** **15**

(a) See Table 1

The result of this investigation is a highly efficient four-step synthesis of the protected 5-*syn*-carboxy-2,4-methanopyrrolidine **12** that also provides access to the previously unreported 5-*anti*-carboxy-2,4-methanopyrrolidine **13**.

(11) (a) Calculations at the B3LYP/6-31G(d) level with Gaussian 98W indicate syn-ketone **10** to be 0.8 kcal/mol more stable than anti-ketone **11**. See the Supporting Information. (b) To determine if the ketone isomerized during the photochemical event, the stereochemistry of the photochemical reaction of purified **7** was monitored. After 2.5 h (67% conversion) an 88:12 ratio of ketones **10**:**11** was found by comparing both the methyl and H_5 peaks of the individual isomers. After 6 h (100% conversion) the same 88:12 ratio was noted. Chromatographic separation resulted in a 94:6 ratio of ketones (72% yield) showing some loss on silica gel. Independently, pure 5-syn-ketone **10** (55 mg) was irradiated in a 0.01 M solution of MeCN for 3.5 h. No stereochemical isomerization was observed and **10** was quantitatively recovered.

(12) The photoirradiation of enamides gives mixed stereochemical results. Photoirradiation of cyclohexane solutions of the *N*-acetyl-*N*-allylenamide of 5,5-dimethyl-1,3-cyclohexanedione, in which the nitrogen and carbonyl groups are constrained to be trans, results in mainly 5-*syn*-keto-2-azabicyclo[2.1.1]hexane photoproducts. Base-catalyzed isomerization converts the 5-syn-isomer to the 5-anti-isomer, but also gives ring cleavage product. See ref 7a and: Tamura, Y.; Kita, Y.; Ishibashi, H.; Ikeda, M. *Tetrahedron Lett.* **1972**, *13*, 1977. By contrast, if the allylic double bond is constrained to a six-membered ring, 5-*anti*-keto isomers, or mainly these isomers, are isolated and the stereochemistry of the enamide is retained. See refs 8 and 9.

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The decarboxylation of **12** has resulted in a 5-step procedure, amenable to multigram scale-up, for preparing N-BOC methanopyrrolidine **2**, a useful synthon for 1- and 3-substituted-2-azabicyclo[2.1.1]hexanes. Further chemistry of the easily prepared synthons **2**, **12**, and **13**, presursors of a wide array of novel 2,4-methanopyrrolidines, will be reported in due course.

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Supporting Information Available: The tables of crystal data, bond lengths and angles, atomic coordinates, and anisotropic thermal parameters accompany the ORTEP drawing for acid **12**; all experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra for new compounds; ^{1}H NMR spectra for enamide **7** and ketones **10** and **11**.[10] This material is available free of charge via the Internet at http://pubs.acs.org.

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