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Efficient preparation of 2,4-methanoproline

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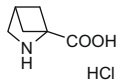
ABSTRACT

Using a modification of the route described by Clardy and Hughes et al., 2,4-methanoproline hydrochloride (**1**) was prepared in four steps and 70% overall yield from DL-serine methyl ester.

Since isolation of 2,4-methanoproline from the seeds of *Ateleia herbert-smithii* Pittier,[1] 2-azabicyclo[2.1.1]hexane scaffolds have generated considerable synthetic, agrochemical, and pharmaceutical interest.[2] As part of our efforts to prepare heterobicyclic inhibitors of glycine transporter 1 (GlyT1), we desired a scalable, short, high-yielding synthesis of 2,4-methanoproline hydrochloride (**1**).



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At the time of this work, existing routes to 2,4-methanoproline varied in length from three to six steps, and yields, with one exception, were typically on the order of 10–20% (Table 1).[3] The most concise route was that of Pirrung, which relied on a photochemical [2+2] cycloaddition (entry 1).[4] The overall yield for this sequence was low due to unoptimized formation of a requisite vinyl allyl amine in 22% yield.[5] Both routes of Stevens et al. also relied on [2+2] cycloadditions. The resulting cyclobutanone precursors were subjected to either a Bucherer-Bergs (entry 2)[6] or a Strecker (entry 3)[2a,b] reaction to enable late stage intramolecular cyclization.

The formal synthesis of Krow et al. (entry 4) employed a bromohydrin rearrangement to generate the 2-azabicyclo[2.1.1]hexane moiety of **1** and was the only route to install the requisite carboxylate via lithiation.[7,8] While the latter was high yielding, the overall yield for this route was similar to those in entries 1–3.

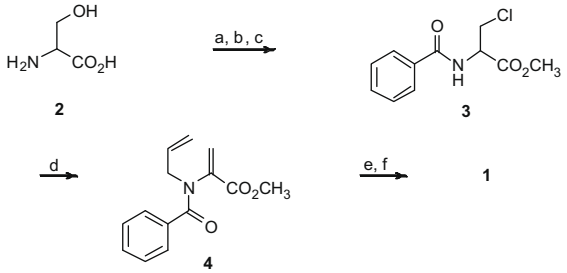
The route devised by Clardy and Hughes et al.,[9] which used a strategy analogous to entry 1, is the highest yielding route of Table 1. An elegant feature of this synthesis is a one-pot dehydrohalogenation/amide allylation of chloride **3** to provide acrylate **4** in excellent yield (Scheme 1). We were encouraged by high yields, the ability to carry forward crude **4** without purification (desirable on large scale) and the lack of cyanide-containing reagents. This route could also be shortened if started from commercially available DL-serine methyl ester (**5**; Aldrich).

In related studies, we examined a two-step transformation of **5** into methyl 2-benzamidoacrylate (**7**; Scheme 2).[10] Both hydroxyl activation and amine protection are accomplished through bisacylation with benzoyl chloride to provide benzoate **6**. Crude **6** can be converted to **7** directly upon treatment with base. We the-

Table 1
Precedented routes to 2,4-methanoproline

Entry	Starting material	Key step(s)[a]	Steps	Yield (%)	Ref
1	Ethyl pyruvate	A	3	19	2c,4
2	Allyl benzyl ether	A, B	5	10	6
3	Allyl chloride	A, B	5	19	2a,2b
4	Pyridine	C, D	6[b]	11[c]	7,8
5	Serine	A	6	68	9

[a] A = [2+2] cycloaddition; B = intramolecular ring closure; C = bromohydrine rearrangement; D = lithiation.
[b] Formal synthesis.
[c] Yield approximated based on starting material differences and an assumed quantitative Boc deprotection.



Reagents: (a) HCl, MeOH; (b) CH_3COCl, PCl_5; (c) $PhCOCl,K_2CO_3$, H_2O/Dioxane, 83%, three steps; (d) KO*t*Bu, Allyl Br, THF, 94%. (e) *hv*, acetophenone, C_6H_6, 87%; (f) 6 N HCl, 98%.

Scheme 1. Route of Clardy and Hughes et al. to **1**.[9]

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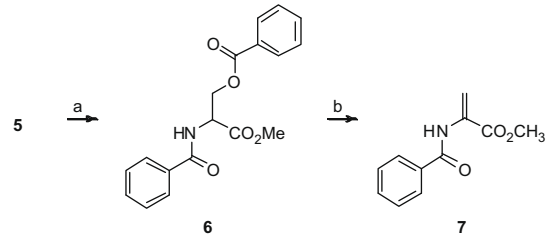
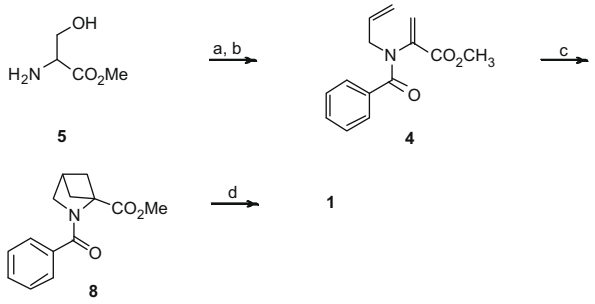


Scheme 2. Route of Avenoza et al. to methyl 2-benzamidoacrylate.[10]



Scheme 3. Reagents: (a) PhCOCl, Et_3N, CH_2Cl_2, 94%; (b) NaH, allyl Br, DMF, 85%; (c) *hν*, acetophenone, CH_3CN, 88%; (d) 6 N HCl, 99%.

orized that benzoate **6** could be substituted for chloride **3**.[11,12] Gratifyingly, acrylate **4** was subsequently obtained in 48% yield employing the procedure of Hughes et al. (Table 2, entry 1).[9b]

We examined modifications to both improve the yield of methyl 2-(*N*-allylbenzamido)acrylate and make the reaction amenable to scale up. In-house experience with **7** indicated that methyl 2-benzamidoacrylate polymerizes upon exposure to strong base. When the reaction concentration was decreased to avoid potential side reactions of this nature, yields increased by 11% (entry 2). Decreasing the quantity of allyl bromide was also tolerated. No improvement was observed when solid potassium *tert*-butoxide was substituted for commercial sources of KO*t*Bu in tetrahydrofuran (entry 3), although fewer byproducts were detected in the crude reaction mixture based on thin-layer chromatography (TLC) analysis.

Reversing the order of addition and maintaining strict control of reaction temperature had little effect (entry 4). However, we determined through reaction monitoring by LC–MS that elimination was complete upon warming to −40 °C following the addition of the first equivalent of potassium *tert*-butoxide. In contrast, alkylation did not appreciably progress until the internal reaction temperature reached 18–23 °C. We hypothesized that generation of **6** could be expedited using a higher starting reaction temperature. A 64% yield was obtained when preparation of **4** was carried out at 0–23 °C.

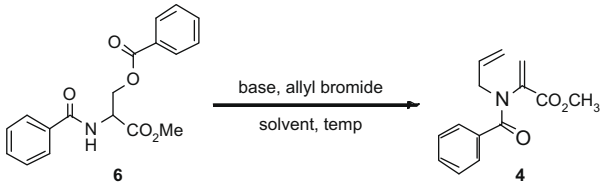
Yields improved when sodium hydride was substituted for potassium *tert*-butoxide (entry 6).[13] This reaction scaled readily with only a slight decrease in yield (entry 7). A drawback of using sodium hydride was the formation of significant precipitate upon addition, necessitating the use of mechanical stirring, and/or, as in the case of entry 8, additional solvent to facilitate mixing.

It should be noted that generation of benzoate **6** on large scale (100+ g) was accompanied by formation (12–16%) of **7** due to the presence of triethylamine upon concentration following workup.[14] We had previously determined that **7**, while prone to polymerization, can also be alkylated using sodium hydride and allyl bromide (data not shown). We concluded that crude benzoate **6**, which might contain acrylate **7** in varying amounts, could be used to prepare **4** directly, obviating the need for flash column chromatography. Entry 8 demonstrates that this is indeed the case.

Acrylate **4** was converted into **1** according to the procedures of Hughes et al. with slight modification (Scheme 3).[9b] Acetonitrile was substituted for benzene during irradiation, improving safety and handling considerations. Hydrolysis of **8** progressed smoothly at 80–100 °C,[15] and concentration yielded 2,4-methanoproline hydrochloride of sufficient purity for further experiments.[16]

In conclusion, we have demonstrated an efficient synthesis of **1** from DL-serine methyl ester in four steps and 70% yield. This route was adapted for the synthesis of batches of 2,4-methanoproline hydrochloride on 20+ g scale, enabling the development of project SAR.

Table 2
Reaction conditions for the transformation of **6** to **4**



Entry	Scale (g)	Base	Equiv (base)	Equiv (AllylBr)	Temp (°C)	Time (h)	Solvent	Conc (M)	Yield (%)	Addition Notes
1	1	KO*t*Bu[a]	2.15	20	−78 to 23	0.75	THF	0.16	48	Procedure according to Ref. 9b.
2	1	KO*t*Bu[a]	2.15	7.2	−78 to 23	1.5	THF	0.08	59	Procedure according to Ref. 9b.
3	1	KO*t*Bu[b]	2.15	6	−78 to 23	16	THF	0.10	51	Procedure according to Ref. 9b.
4	1	KO*t*Bu[a]	2.30	6	−78 to −40; −78 to 23	16	THF	0.10	57	Addition of base to **6** at −78 °C, warming to −40 °C; 2nd equiv of base added at −78 °C followed rapidly by allyl bromide.
5	1	KO*t*Bu[a]	2.9	6	0 to 23	16	THF	0.20	64	Addition of base to **6** at 0 °C followed rapidly by allyl bromide
6	0.4	NaH[c]	2.05	12	23	0.5	DMF	0.09	85	Addition of base to both allyl bromide and **6** at 23 °C
7	11	NaH[c]	2.15	15	23	1.5	DMF	0.09	78	Addition of NaH to both allyl bromide and **6** at 23 °C
8	21[d]	NaH[c]	2.25	12	0 to 23	2.0	DMF	0.2 to 0.15	78	Addition of NaH to both allyl bromide and **6** at 0 °C; internal temp rose to 13 °C during addition

[a] 1.0 M solution in tetrahydrofuran.
[b] Solid KO*t*Bu.
[c] 60% dispersion in mineral oil.
[d] Crude starting material (**6**).

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12. *Preparation of 2-benzamido-3-methoxy-3-oxopropyl benzoate* (**6**; derived from Ref. 10): Benzoyl chloride (8.57 mL, 73.9 mmol) was added dropwise to a solution of DL-serine methyl ester hydrochloride (5.0 g, 32.1 mmol) and triethylamine (15.2 mL, 109 mmol) in dichloromethane (137 mL) while maintaining a reaction temperature between 5 and 10 °C. The resulting white mixture was warmed to 23 °C and stirred for 1.5 h before being washed with saturated aqueous sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and concentrated to an off-white solid. Purification via flash column chromatography (SiO_2, 0–50% ethyl acetate in hexanes) afforded **6** (9.90 g, 94%) as a white solid. ^{1}H NMR (500 MHz, chloroform-*d*) δ (ppm) 7.98–8.02 (m, 2H), 7.78–7.84 (m, 2H), 7.55–7.60 (m, 1H), 7.49–7.54 (m, 1H), 7.40–7.47 (m, 4H), 7.04 (d, J = 7.0 Hz, 1H), 5.18 (dt, J = 7.5, 3.9 Hz, 1H), 4.74–4.82 (m, 2H), 3.83 (s, 3H). MS (ESI$^+$), (M+H)$^+$ = 328.2.
13. *Preparation of methyl 2-(N-allylbenzamido)acrylate* (**4**) *from* **6**: To a solution of 2-benzamido-3-methoxy-3-oxopropyl benzoate (0.40 g, 1.22 mmol) and allyl bromide (1.27 mL, 14.7 mmol) in DMF (12 mL) was added sodium hydride (0.10 g, 2.5 mmol) as a 60% dispersion in mineral oil in one portion. *Caution*: Exothermic reaction with evolution of a flammable gas! The clear colorless solution rapidly became a yellow mixture. The mixture became a lighter yellow over 30 min and was then diluted with water and extracted with ethyl acetate (×3). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The resulting residue was purified by flash column chromatography (SiO_2, 0–20% ethyl acetate in hexanes) to afford **4** (0.25 g, 85%) as a clear colorless oil. ^{1}H NMR (500 MHz, Chloroform-*d*) δ (ppm) 7.43–7.53 (m, 2H), 7.35–7.41 (m, 1H), 7.30–7.36 (m, 2H), 6.07 (s, 1H), 5.86–5.96 (m, 1H), 5.50 (s, 1H), 5.18–5.27 (m, 2H), 4.31 (d, J = 5.8 Hz, 2H), 3.63 (s, 3H). MS (ESI$^+$), (M+H)$^+$ = 328.2. *Note*: Addition of base for reactions between 1 and 20 g scale was successful at 0 °C with portion-wise addition of sodium hydride and careful monitoring of internal reaction temperature. For reactions involving over 20 g of **6**, reaction vessels were precharged with allyl bromide and NaH in DMF prior to addition of benzoate **6** at 0 °C, also as a solution in DMF. Mechanical stirring and reaction concentrations of 0.1 M or less are strongly recommended.
14. It was necessary to use a 0.5 N hydrochloric acid wash during workup to remove excess triethylamine in order to prevent significant formation of methyl 2-amidoacrylate (**7**) during concentration of organic layers containing crude **6**. Crude 2-benzamido-3-methoxy-3-oxopropyl benzoate (**6**) can also be purified by recrystallization as follows: Crude **6** (137 g) in ethyl acetate (500 mL) was heated to near reflux conditions (74 °C) over 30 min. To the resulting yellow solution was added dropwise over 5 min 500 mL of hexanes that had been preheated to 70 °C. The resulting mixture was maintained at reflux conditions for 5 min and then cooled. Following filtration, the filter cake was washed with 300 mL of 40% ethyl acetate in hexanes before being dried in vacuo at 50 °C. Yield: 101 g (74%). Concentration of the filtrate afforded 37 g of **6** that could be further recrystallized as mentioned above.
15. Lower reaction temperatures required longer reaction times based on LC–MS reaction monitoring. For example, hydrolysis of **8** (using the procedure of Ref. 9b) carried out at 100 °C was typically complete after 2.5 h; hydrolysis at 80 °C required 7.5 h to achieve completion.
16. An effective purification (via trituration) of crude **1** on scale is as follows: A suspension of crude 2,4-methanoproline hydrochloride (43.2 g, from concentration of the hydrolysis reaction in Scheme 3; >100% yield due to the presence of residual water) and reagent-grade acetone (100 mL) was stirred for 15 min and then filtered. The filter cake was washed with 10% ethanol in acetone (2 × 50 mL) and dried in vacuo at 45–50 °C to afford **1** (23.3 g, 71%) as a white powder. Filtrates could be concentrated and reprocessed as mentioned above. ^{1}H NMR (methanol-d_4, 300 MHz): δ (ppm) 3.44 (s, 2H), 2.97 (t, J = 3.3 Hz, 1H), 2.38–2.58 (m, 2H), 1.70–1.92 (m, 2H).