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Tetrahedron
Tetrahedron 61 (2005) 1579–1586

The synthesis of baclofen and GABOB via Rh(II) catalyzed intramolecular C–H insertion of α-diazoacetamides

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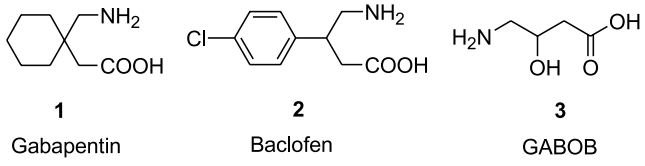
Received 15 March 2004; revised 14 November 2004; accepted 15 November 2004

Available online 18 December 2004

Abstract—The synthesis of baclofen and GABOB is reported via hydrolysis of the corresponding *N-tert*-butyl γ-lactams, which were obtained from Rh(II) catalyzed intramolecular C–H insertion of α-diazoacetamides.

1. Introduction

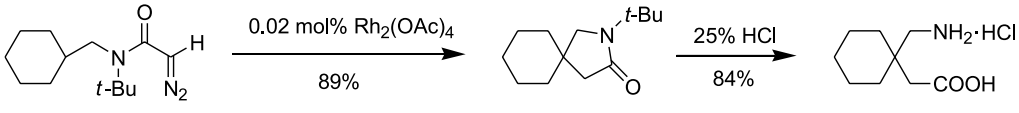
γ-Amino butyric acid (GABA) is an important central nervous system neurotransmitter.[1] It has profound impact on many important biological functions. Hence, GABA analogues, such as gabapentin,[2] baclofen[3] and γ-amino β-hydroxy butyric acid (GABOB)[4] (Fig. 1), have been well explored as medicines to treat various diseases associated with GABA receptors. For instance, gabapentin (**1**) has been used for the treatment of cerebral diseases such as epilepsy, faintness attacks, hypokinesis and cranial traumas.[2b] Although many methods have been developed for the preparation of GABA analogues,[1–4] there is still increasing interests for general and practical synthetic approaches.



1 Gabapentin **2** Baclofen **3** GABOB

Figure 1.

In the transition metal catalyzed C–H insertion of α-diazoacetamide, regioselectivity has remained a major challenge. It has been well documented that regioselectivity depends highly on the substitutents of diazo carbon, the *N*-substitutents on the amide moiety, and the electrophilicity of the catalysts.[5] In the past twenty years, some examples have been reported on the application of the intramolecular C–H insertion of α-diazoacetamide.[6] High regioselectivity has been achieved with *N-tert*-butyl α-diazoacetamide, initially reported by Padwa and co-workers.[7] In our previous communication, we found that the *tert*-butyl protecting group can be easily removed in hydrochloric acid and gabapentin (**1**) was prepared accordingly (Scheme 1).[7e] Excellent selectivity and high reactivity of *N-tert*-butyl α-diazoacetamides shed lights on the potential application as a general method to other GABA analogues. We report here our detail study of this approach towards β-substituted GABA analogues such as (±)-baclofen (**2**) and (±)-GABOB (**3**) (Scheme 2).



4 **5** **1**

Scheme 1.

Keywords: C–H Insertion; γ-Lactam; Gabapentin; Baclofen; GABA.
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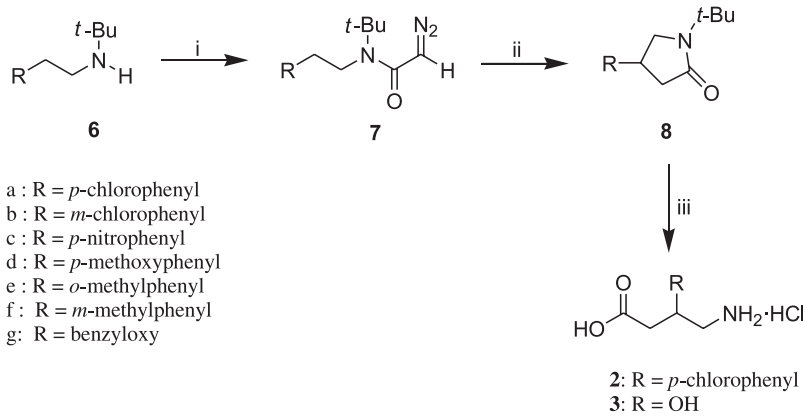
doi:10.1016/j.tet.2004.11.077



Scheme 2. (i) Diketene, THF; *p*-ABSA, DBU, THF; LiOH, H_2O, THF, 75–86% yield. (ii) $Rh_2(cap)_4$ (1 mol%), refluxing CH_2Cl_2, 55–94% yield. (iii) **2**: 28% HCl, reflux, 95% yield; **3**: 25% HCl, 90 °C, 95% yield.

2. Results and discussion

2.1. Preparation of GABA analogues

α-Diazoacetatamides (**7**) were prepared from *N*-*tert*-butyl amine (**6**) according to the literature procedure.[8] Catalyzed by 1 mol% of $Rh_2(cap)_4$, intramolecular C–H insertion of **7** gave corresponding γ-lactam (**8**) in good yield and excellent regioselectivity. Hydrolysis of γ-lactam **8** under refluxing aqueous HCl afforded the desired β-substituted GABA products as corresponding hydrochloride salt (Scheme 2). In this way, *tert*-butyl protecting group was easily introduced and removed (Table 1).

Table 1. Synthesis of α-diazoacetamides (**7**) and γ-lactams (**8**)[a]

Entry	R	Yield of **7** (%)	Yield of **8** (%)
1	*p*-Chlorophenyl	84	77
2	*m*-Chlorophenyl	77	65
3	*p*-Nitrophenyl	77	55 (61)[b]
4	*p*-Methoxphenyl	75	71 (68)[b]
5	*o*-Methylphenyl	81	88
6	*m*-Methylphenyl	81	74
7	Benzyloxy	86	94

[a] Isolated yield after column chromatography purification.
[b] The yield was reported in literature **7b** (catalyzed by $Rh_2(OAc)_4$).

2.2. Catalyst effect

In the intramolecular C–H insertion of the α-diazoacetamides, the choice of the catalysts was important. Intramolecular C–H insertion of α-diazoacetamide (**7a**) with $Rh_2(cap)_4$ gave γ-lactam (**8a**) in 77% yield, while only 51% yield was obtained with $Rh_2(OAc)_4$. In addition to Rh(II) catalyst, $Cu(OTf)_2$ was also effective to catalyze the reaction, however, in lower yield (Table 2). Low yield of **8a** compared with **5** and **8g** was due to a side reaction, namely aromatic cycloaddition, which was suppressed by using $Rh_2(cap)_4$ catalyst.

2.3. Catalyst efficiency and substrate reactivity

The catalytic efficiency of this C–H insertion process was examined by lowering catalyst loading of dirhodium acetate (Table 3). For α-diazoacetamide (**4**), with substrate/catalyst ratio of 5000, γ-lactam (**5**) was obtained in 89% yield.[7e] When the same catalyst loading applied to **7g**, γ-lactam (**8g**) was obtained in 68% yield with 25% starting material recovered, thus reaction with even lower catalyst loading was not further examined.

Table 3. Dirhodium acetate catalyzed C–H insertion of α-diazoacetamides (**4** and **7g**) with different catalyst loading[a]

Entry	Substrate/catalyst	Yield of **5** (%)[b]	Yield of **8g** (%)[b]
1	100	95	91
2	500	88	89
3	1000	89	78[c]
4	5000	89	68[c]

[a] Reactions were carried out in refluxing CH_2Cl_2 for 3 h according to the general experimental procedure.
[b] Isolated yield after column chromatography purification.
[c] Reactions were carried out in refluxing CH_2Cl_2 for 12 h according to the general experimental procedure.

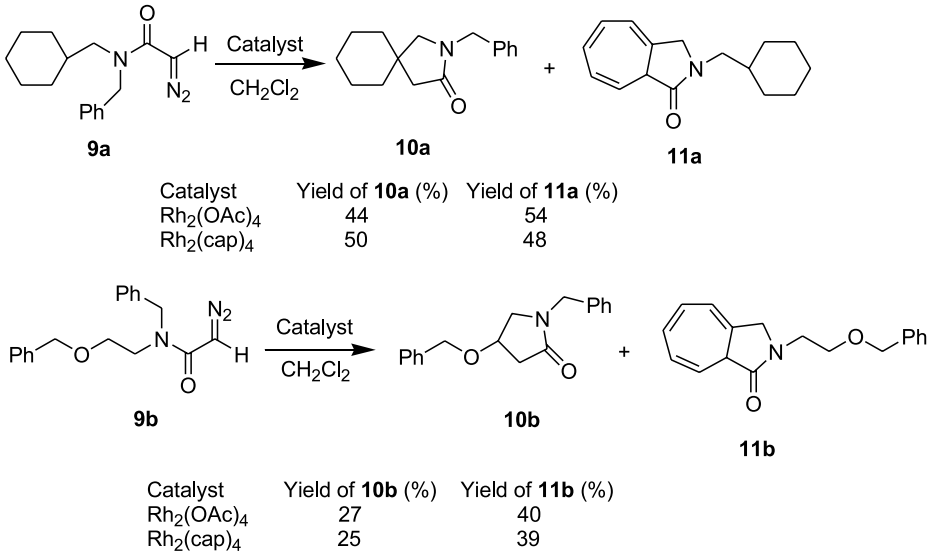
2.4. The effect of nitrogen protecting group on regioselectivity

Other *N*-protecting groups such as *p*-methoxyphenyl,[9a] *p*-nitrophenyl,[6a] and BTMSM (bis(trimethyl-silyl)methyl)[9b] have been reported in the intramolecular C–H insertion of α-diazoacetamides. In order to further demonstrate the effect of *N*-protecting group on regioselectivity of the C–H insertion, *N*-benzyl protected α-diazoacetamides (**9a** and

Table 2. Catalyst effect on intramolecular C–H insertion of α-diazoacetamides[a]

Entry	Catalyst	Yield of **5** (%)[b]	Yield of **8a** (%)[b]	Yield of **8g** (%)[b]
1	$Rh_2(OAc)_4$	95	51	91
2	$Rh_2(cap)_4$	96	77	93
3	$Cu(OTf)_2$	88	31	79

[a] All the reactions were carried out in refluxing CH_2Cl_2 for 3 h according to general experimental procedure.
[b] Isolated yield after column chromatography purification.



Scheme 3.

9b) were subjected to diazo decomposition in the presence of 1 mol% of dirhodium acetate. The desired γ-lactam (**10**) was obtained in only 44% (**10a**) and 27% (**10b**) yield, respectively. The major side reaction was found to be the intramolecular aromatic cycloaddition reaction, in which attacking of metal carbene to the benzyl protecting group occurred producing compound **11** in 54% (**11a**) and 40% (**11b**) yield, respectively (Scheme 3). The side reaction also occurred with $Rh_2(cap)_4$ (Scheme 3). In contrast, there was no side reaction occurred to the *N*-*tert*-butyl protecting group in α-diazoacetamides (**4** and **7**).

2.5. Hydrolysis of γ-lactams

TfOH[10a] and H_2SO_4[10b] have been successfully used to remove *N*-*tert*-butyl group from amides or carbamates. Unfortunately, by using the similar procedures, we were unable to obtain either deprotected product of **5** or the desired product **1**. However, aqueous hydrochloric acid was found to be effective to remove the *tert*-butyl group in our previous investigation,[7e] where the lactam ring was opened simultaneously to give the corresponding hydrochloride salt. Applying this protocol to hydrolyze γ-lactam **8g**, the debenzylation occurred with the γ-lactam ring opening and further dehydration was a side reaction producing α,β-unsaturated γ-amino butyric acid (**12**). Fortunately, the dehydration was found to be temperature dependent (Table 4). At 90 °C (oil bath temperature), (±)-GABOB hydrochloride salt was obtained in 95% yield. Compound **3** and **12** can be readily separated by the preparation of the corresponding *N*-Boc derivatives (*N*-Boc-GABOB (**13**) and *N*-Boc-**12**).

3. Conclusion

We have described a new approach for the synthesis of (±)-baclofen and (±)-GABOB from ring opening of γ-lactams, which were obtained in good yield from Rh(II) (1 mol%) catalyzed intramolecular C–H insertion of *tert*-butyl protected α-diazoacetamides. Given the successful γ-lactam formation from other *N*-*tert*-butyl α-diazoacetamides reported in the literature,[7a,b] this approach can be a general method for the synthesis of β-substituted γ-amino butyric acid.

4. Experimental

4.1. General methods

NMR spectra were recorded on a Bruker-300 MHz spectrometer. HRMS (ESI) mass spectra were recorded on BRUKER FT-MS. Mass spectra were recorded on a VG7070E instrument. Infrared spectra were measured on a Nicolet 200SXV FT-IR spectrometer. Melting points were determined on a digital melting point apparatus and uncorrected. Dichloromethane and dimethyl sulfoxide were distilled over calcium hydride. Tetrahydrofuran was distilled over sodium. *N*,*N*-Dimethylformamide was dried over 4 Å molecular sieves.

4.1.1. *N*-*tert*-Butyl-*N*-cyclohexylmethyl amine. To cyclohexane carboxaldehyde (5 mL, 40.5 mmol) in ethanol (40 mL) was added *tert*-butyl amine (6.89 mL, 58.5 mmol) and the solution was stirred at room temperature for 1 h. To the solution was added, 5% palladium on

Table 4. Temperature effect on hydrolysis of **8g** with 25% HCl (without any organic solvent)

Entry	Oil bath temperature (°C)	Time (h)	Yield (%)[a]	Ratio of **3**/**12**[b]
1	120	11	89	90/10
2	100	17	93	94/6
3	90	18	95	>95/5

[a] Combined yield of compound **3** (as the corresponding hydrochloride salt) and **12**.
[b] Determined by ^1H NMR.

charcoal catalyst (1.4 g) and followed 1 atm hydrogen. The reaction mixture was stirred at 50 °C for 12 h. After cooling to room temperature, the catalyst was filtered off and the solvent was removed under reduced pressure. The resulting clear oil was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 5:1 v/v) to afforded *N*-*tert*-butyl-*N*-cyclohexylmethyl amine as an colorless oil (6.1 g, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.36 (d, 2H, J= 6.6 Hz), 1.77–1.68 (m, 5H), 1.37–1.16 (m, 5H), 1.08 (s, 9H), 0.90–0.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 50.9, 50.1, 39.6, 32.5, 29.8, 27.6, 26.9; HRMS (ESI) calcd for $C_{11}H_{24}N$ $[M+H]^+$: 170.1909, found: 170.1900.

4.1.2. *N*-*tert*-Butyl-*N*-*p*-chlorophenylethyl amine (6a). To anhydrous *N*,*N*-dimethylformamide (15 mL) was added potassium carbonate (1.6 g, 11.6 mmol). The resulting white suspension was vigorously stirred for 10 min. *tert*-Butyl amine (2.5 mL, 23.6 mmol), *p*-chlorophenylethyl bromide (2.3 g, 10.5 mmol) and potassium iodide (0.1 g, 0.6 mmol) were added to the white suspension in sequence. The reaction mixture was stirred at 60 °C for 24 h. After cooling to room temperature, water (20 mL) and ethyl acetate (30 mL) were added. The aqueous layer was extracted with ethyl acetate (2×30 mL). The combined organic layer was washed with saturated sodium chloride (4×20 mL), dried over sodium sulfate. Solvent was removed under reduced pressure to give a yellow oil. Silica gel column chromatography purification (petroleum ether/ethyl acetate, 2:1 v/v) yield a pale yellow oil (1.1 g, 47% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, 2H, J= 8.3 Hz), 7.09 (d, 2H, J=8.3 Hz), 2.78–2.66 (m, 4H), 1.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 131.6, 129.5, 128.3, 50.1, 43.7, 36.4, 28.8; HRMS (ESI) calcd for $C_{12}H_{19}NCl$ $[M+H]^+$: 212.1206, found: 212.1201.

4.1.3. *N*-*tert*-Butyl-*N*-Benzyloxyethyl amine (6g). An oven dried, 150 mL, one-necked round-bottom flask equipped with a magnetic stirring bar was flashed with argon. Dichloromethane (50 mL) was added. The flask inlet was sealed with a rubber septum and cooled to 0 °C in an ice bath. To this flask was added triethylamine (3.5 mL, 25 mmol), benzyloxyethyl alcohol (3.1 g, 20.4 mmol) and methanesulfonyl chloride (2 mL, 25.8 mmol). The resulting solution was stirred at room temperature for 2 h and then quenched by adding 20 mL ice water. The organic layer was separated and washed successively with saturated aqueous sodium bicarbonate (20 mL) and brine (2×20 mL). The organic layer was dried over magnesium sulfate, filtered and concentrated with a rotary evaporator to give crude benzyloxyethyl methanesulfonate. The crude methanesulfonate was directly used in the next step without further purification. To another oven dried, 100 mL, one necked round-bottom flask containing a magnetic stirring bar and a rubber septum inlet was flashed with argon and charged with potassium iodide (200 mg). The crude methanesulfonate in dimethyl sulfoxide (20 mL) was added to the flask and followed by addition of *tert*-butyl amine (6 mL, 56.8 mmol). The resulting solution was stirred at 50 °C for 8 h and then allowed to cool to room temperature. The reaction solution was poured into a separatory funnel containing 30 mL of 1% aqueous sodium hydroxide. The resulting mixture was extracted with ethyl acetate (2× 30 mL). The combined organic layer are washed with brine (4×20 mL), dried over sodium sulfate, filtered and concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate, 5:1 v/v) to give *N*-*tert*-butyl-*N*-benzyl-oxyethyl amine (**6g**) (2.8 g, 66% yield). Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 4.46 (s, 2H), 3.54 (*t*, 2H, J=5.4 Hz), 2.71 (*t*, 2H, J=5.4 Hz), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.4, 127.7, 127.6, 73.1, 70.6, 49.9, 42.2, 28.9; HRMS (ESI) calcd For $C_{13}H_{22}NO$ $[M+H]^+$: 208.1701, found: 208.1689.

Other *N*-*tert*-butyl amines (**6b–6f**) were prepared in a similar manner.

4.1.4. *N*-*tert*-Butyl-*N*-*m*-chlorophenylethyl amine (6b). Yield 31.5%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24–7.08 (m, 4H), 2.84–2.71 (m, 4H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2, 134.0, 129.5, 128.6, 126.7, 126.2, 50.2, 43.7, 36.8, 28.9; HRMS (ESI) calcd for $C_{12}H_{19}NCl$ $[M+H]^+$: 212.1206, found: 212.1201.

4.1.5. *N*-*tert*-Butyl-*N*-*p*-nitrophenylethyl amine (6c). Yield: 55.7%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.15 (dt, 2H, J=9.2, 2.2 Hz), 7.37 (dt, 2H, J=9.2, 2.2 Hz), 2.86 (s, 4H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 146.6, 129.5, 123.6, 50.4, 43.5, 37.2, 28.9.

4.1.6. *N*-*tert*-Butyl-*N*-*p*-methoxyphenylethyl amine (6d). Yield 49.5%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15–7.11 (m, 2H), 6.86–6.81 (m, 2H), 3.78 (s, 3H), 2.82–2.77 (m, 2H), 2.73–2.68 (m, 2H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 132.2, 129.5, 113.8, 55.2, 50.2, 44.2, 36.3, 28.9.

4.1.7. *N*-*tert*-Butyl-*N*-*o*-methylphenylethyl amine (6e). Yield 49.8%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.11 (m, 4H), 2.78 (s, 4H), 2.33 (s, 3H), 1.1 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.2, 130.2, 129.0, 126.2, 125.9, 50.3, 42.9, 34.9, 29.0, 19.4.

4.1.8. *N*-*tert*-Butyl-*N*-*m*-methylphenylethyl amine (6f). Yield 45.1%. Yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22–7.16 (m, 1H), 7.04–7.01 (m, 3H), 2.86–2.80 (m, 2H), 2.77–2.72 (m, 2H), 2.34 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.1, 129.6, 128.4, 126.9, 125.8, 50.4, 44.3, 37.3, 29.1, 21.5.

4.1.9. *N*-Benzyl-*N*-cyclohexylmethyl amine. Yield 42%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 5H), 3.77 (s, 2H), 2.46 (d, 2H, J=6.6 Hz), 1.77–1.68 (m, 5H), 1.47–1.19 (m, 5H), 0.91–0.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 128.3, 128.0, 126.7, 56.2, 54.2, 38.0, 31.4, 26.7, 26.0.

4.1.10. *N*-Benzyl-*N*-benzyloxyethyl amine. Yield 24%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37–7.22 (m, 10H), 4.52 (s, 2H), 3.80 (s, 2H), 3.62 (*t*, 2H, J=5.2 Hz), 2.84 (*t*, 2H, J=5.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.3, 128.4, 128.3, 128.1, 127.7, 127.6, 126.9, 73.2, 69.7, 53.9, 48.8.

4.1.11. *N*-*tert*-Butyl-*N*-cyclohexylmethyl α-diazoacetamide (4). To *N*-*tert*-butyl-*N*-cyclohexylmethyl amine

(4.3 g, 25 mmol) in tetrahydrofuran (30 mL) was added diketene (2 mL, 25 mmol). The mixture was stirred at 0 °C for 0.5 h, then allowed to warm to room temperature and stirred overnight. To the resulting brown reaction mixture was added 4-acetamidobenzene sulfonyl azide (7.3 g, 29 mmol), followed by adding of 1,8-diazabicyclo[5,4,0] undec-7-ene (4.4 mL, 29 mmol). The resulting solution was stirred at room temperature for 8 h. A solution of lithium hydroxide ($LiOH \cdot H_2O$, 4 g, 95 mmol) in water (50 mL) was added and the resulting orange-brown mixture was stirred vigorously for 8 h. The reaction mixture was diluted with ethyl acetate (60 mL) and the organic layer was washed with water (2×30 mL), dried over $MgSO_4$. Solvent was removed under reduced pressure to yield a red-brown mixture. Silica gel column chromatography (petroleum ether/ethyl acetate, 5:1 v/v) yield a yellow solid (4.6 g, 77% overall yield from *N*-*tert*-butyl-*N*-cyclohexylmethyl amine), mp: 73.6–74.7 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (s, 1H), 2.93 (d, 2H, $J=7.2$ Hz), 1.78–1.75 (m, 5H), 1.37–1.34 (m, 1H), 1.47 (s, 9H), 1.25–1.16 (m, 3H), 0.89–0.86 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 57.5, 51.2, 48.9, 39.7, 30.8, 29.0, 26.1, 25.9; FT-IR (KBr, cm^{-1}): 2113 (C=O); HRMS (ESI) calcd for $C_{13}H_{24}N_3O$ $[M+H]^+$: 238.1919, found: 238.1918.

Other α-diazoacetamides (**7a**–**7b**) and (**9a**–**9b**) were prepared in a similar manner.

4.1.12. *N*-*tert*-Butyl-*N*-*p*-chlorophenylethyl α-diazoacetamide (7a). Yield: 84% overall yield from *N*-*tert*-butyl-*N*-*p*-chlorophenylethyl amine (**6a**), yellow solid, mp: 113.5–114.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.13–7.11 (m, 2H), 4.95 (s, 1H), 3.31 (t, 2H, $J=7.4$ Hz), 2.83 (t, 2H, $J=7.4$ Hz), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 141.2, 132.7, 128.9, 128.0, 54.2, 52.9, 40.5, 36.4, 27.7; FT-IR (KBr, cm^{-1}): 2100 (C=N_2); HRMS (ESI) calcd for $C_{14}H_{19}N_3ClO$ $[M+H]^+$: 280.1217, found: 280.1218.

4.1.13. *N*-*tert*-Butyl-*N*-*m*-chlorophenylethyl α-diazoacetamide (7b). Yield: 76.8% overall yield from *N*-*tert*-butyl-*N*-*m*-chlorophenylethyl amine (**6b**), yellow solid, mp: 92.2–93.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29–7.04 (m, 4H), 4.97 (s, 1H), 3.33–3.27 (m, 2H), 2.84–2.79 (m, 2H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 140.2, 134.6, 130.1, 128.5, 127.0, 126.6, 57.9, 48.7, 46.6, 37.6, 29.4; FT-IR (KBr, cm^{-1}): 2099 (C=N_2); HRMS (ESI) calcd for $C_{14}H_{19}N_3ClO$ $[M+H]^+$: 280.1217, found: 280.1218.

4.1.14. *N*-*tert*-Butyl-*N*-*p*-nitrophenylethyl α-diazoacetamide (7c). Yield: 77.3% overall yield from *N*-*tert*-butyl-*N*-*p*-nitrophenylethyl amine (**6c**), yellow solid, mp: 148.3–149.3 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (dt, 2H, $J=9.2$, 2.2 Hz), 7.35 (dt, 2H, $J=9.2$, 2.2 Hz), 4.97 (s, 1H), 3.39–3.33 (m, 2H), 2.99–2.93 (m, 2H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 146.9, 145.9, 129.3, 124.1, 57.8, 48.9, 46.2, 37.7, 29.5; FT-IR (KBr, cm^{-1}): 2106 (C=N_2).

4.1.15. *N*-*tert*-Butyl-*N*-*p*-methoxyphenylethyl α-diazoacetamide (7d). Yield: 74.6% overall yield from *N*-*tert*-butyl-*N*-*p*-methoxyphenylethyl amine (**6e**), yellow solid, mp: 70.5–71.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10–7.06 (m, 2H), 6.88–6.84 (m, 2H), 4.96 (s, 1H), 3.79 (s, 3H), 3.29–3.23 (m, 2H), 2.80–2.75 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 158.4, 130.3, 129.4, 114.2, 57.8, 55.3, 48.6, 47.2, 37.1, 29.3; FT-IR (KBr, cm^{-1}): 2113 (C=N_2).

4.1.16. *N*-*tert*-Butyl-*N*-*o*-methylphenylethyl α-diazoacetamide (7e). Yield: 81.1% overall yield from *N*-*tert*-butyl-*N*-*o*-methylphenylethyl amine (**6e**), yellow solid, mp: 72.2–73.2 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.11 (m, 4H), 5.01 (s, 1H), 3.32–3.26 (m, 2H), 2.88–2.83 (m, 2H), 2.37 (s, 3H), 1.53 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 136.8, 135.8, 130.6, 129.0, 126.9, 126.4, 57.9, 48.6, 45.7, 35.3, 29.4, 19.7; HRMS (ESI) calcd for $C_{15}H_{22}N_3O$ $[M+H]^+$: 260.1764, found: 260.1763.

4.1.17. *N*-*tert*-Butyl-*N*-*m*-methylphenylethyl α-diazoacetamide (7f). Yield: 80.7% overall yield from *N*-*tert*-butyl-*N*-*m*-methylphenylethyl amine (**6f**). Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26–7.19 (m, 1H), 7.08–7.05 (m, 1H), 6.98–6.96 (m, 2H), 4.99 (s, 1H), 3.32–3.26 (m, 2H), 2.83–2.77 (m, 2H), 2.35 (s, 3H), 1.52 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 138.5, 138.2, 129.1, 128.7, 127.5, 125.3, 57.8, 48.6, 46.9, 37.9, 29.3, 21.3; HRMS (ESI) calcd for $C_{15}H_{22}N_3O$ $[M+H]^+$: 260.1763, found: 260.1763.

4.1.18. *N*-*tert*-Butyl-*N*-benzyloxyethyl α-diazoacetamide (7g). Yield: 78% overall yield from *N*-*tert*-butyl-*N*-benzyloxyethyl amine (**6g**). Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 5.11 (s, 1H), 4.45 (s, 2H), 3.44 (*t*, 2H, $J=6.3$ Hz), 3.26 (*t*, 2H, $J=6.3$ Hz), 1.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 137.6, 128.4, 127.8, 127.5, 73.3, 70.2, 57.6, 48.4, 44.7, 29.1; FT-IR (KBr, cm^{-1}): 2102 (C=N_2); HRMS (ESI) calcd for $C_{15}H_{22}N_3O$ $[M+H]^+$: 276.1712, found: 276.1711.

4.1.19. *N*-Benzyl-*N*-cyclohexylmethyl α-diazoacetamide (9a). Yield: 75% overall yield from *N*-benzyl-*N*-cyclohexylmethyl amine. Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.19 (m, 5H), 4.94 (s, 1H), 4.45 (wide, 2H), 3.24–2.9 (wide, 2H), 1.71–1.67 (m, 6H), 1.28–1.16 (m, 3H), 0.93–0.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 128.7, 127.4, 53.3, 50.4, 46.9, 37.1, 31.0, 26.3, 25.8; FT-IR (cm^{-1}): 2105 (C=N_2); HRMS (ESI) calcd for $C_{16}H_{22}N_3O$ $[M+H]^+$: 272.1763, found: 272.1761.

4.1.20. *N*-Benzyl-*N*-bezyloxyethyl α-diazoacetamide (9b). Yield: 78% overall yield from *N*-benzyl-*N*-benzyloxyethyl amine. Yellow viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.19 (m, 10H), 5.10 (wide, 1H), 4.57 (s, 2H), 4.47 (s, 2H), 3.47–3.32 (wide, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 137.9, 137.3, 128.7, 128.4, 127.9, 127.7, 127.6, 127.4, 73.3, 67.5, 49.6, 47.1, 46.9; FT-IR (cm^{-1}): 2105 (C=N_2); HRMS (ESI) calcd for $C_{18}H_{20}N_3O_2$ $[M+H]^+$: 310.1556, found: 310.1543.

4.2. General procedure for α-diazoacetamide decomposition

To a solution of $Rh_2(cap)_4$ (1 mol%) in the CH_2Cl_2 (5 mL)

at reflux was added the α-diazoacetamide (1.0 mmol) in the CH_2Cl_2 (5 mL) via a syringe pump over 2 h period. After the addition was complete, the reaction solution was stirred for an additional 30 min, then the solvent was removed under reduced pressure. Silica gel column chromatography purification (petroleum ether/ethyl acetate, 3:1 v/v) yielded the γ-lactam as a pale yellow (or colorless) oil.

4.2.1. *N-tert*-Butyl-β-cyclohexyl-γ-lactam (5). Yield 96%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (s, 2H), 2.20 (s, 2H), 1.46–1.36 (m, 19H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.1, 68.7, 58.3, 54.4, 37.4, 35.9, 28.5, 26.5, 26.4, 23.6; FT-IR (cm^{-1}): 1686 (C=O); HRMS (ESI) calcd for $C_{13}H_{24}NO$ $[M+H]^+$: 210.1858, found: 210.1854.

4.2.2. *N-tert*-Butyl-β-*p*-chlorophenyl-γ-lactam (8a). Yield 77%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, 2H, J=8.4 Hz), 7.18 (d, 2H, J=8.4 Hz), 3.84 (t, 1H, J=8.7 Hz), 3.43–3.34 (m, 2H), 2.76 (dd, 1H, J=16.5, 8.7 Hz), 2.49 (dd, 1H, J=16.8, 8.4 Hz), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 141.2, 132.7, 128.9, 128.0, 54.2, 52.9, 40.5, 36.4, 27.7; FT-IR (cm^{-1}): 1685 (C=O); HRMS (ESI) calcd for $C_{14}H_{19}NClO$ $[M+H]^+$: 252.1155, found: 252.1157.

4.2.3. *N-tert*-Butyl-β-*m*-chlorophenyl-γ-lactam (8b). Yield 65.4%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.21 (m, 3H), 7.13–7.10 (m, 1H), 3.84–3.82 (m, 1H), 3.45–3.36 (m, 2H), 2.75 (dd, 1H, J=16.6, 8.9 Hz), 2.50 (dd, 1H, J=16.6, 8.9 Hz), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 144.7, 134.6, 130.1, 127.1, 126.9, 124.8, 54.2, 52.7, 40.4, 36.7, 27.7; FT-IR (cm^{-1}): 1683 (C=O); HRMS (ESI) calcd for $C_{14}H_{19}NClO$ $[M+H]^+$: 252.1155, found: 252.1157.

4.2.4. *N-tert*-Butyl-β-*p*-nitrophenyl-γ-lactam (8c). Yield 55.4%. Yellow solid, mp: 67.3–68.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (dt, 2H, J=9.2, 2.2 Hz), 7.40 (dt, 2H, J=9.2, 2.2 Hz), 3.91 (dd, 1H, J=9.6, 7.9 Hz), 3.62–3.52 (m, 1H), 3.42 (dd, 1H, J=9.6, 6.6 Hz), 2.83 (dd, 1H, J=16.7, 8.9 Hz), 2.52 (dd, 1H, J=16.7, 7.8 Hz), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 150.3, 146.9, 127.6, 124.1, 54.4, 52.5, 40.3, 36.8, 27.7; FT-IR (KBr, cm^{-1}): 1684 (C=O).

4.2.5. *N-tert*-Butyl-β-*p*-methoxyphenyl-γ-lactam (8d). Yield 71%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18–7.13 (m, 2H), 6.89–6.83 (m, 2H), 3.79 (s, 3H), 3.38–3.35 (m, 2H), 2.73 (dd, 1H, J=16.5, 8.8 Hz), 2.50 (dd, 1H, J=16.6, 8.5 Hz), 1.42 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 158.4, 134.5, 129.6, 127.6, 114.1, 55.2, 53.9, 53.3, 40.9, 36.3, 27.7; FT-IR (KBr, cm^{-1}): 1685 (C=O).

4.2.6. *N-tert*-Butyl-β-*o*-methylphenyl-γ-lactam (8e). Yield 87.9%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27–7.14 (m, 4H), 3.83 (dd, 1H, J=9.5, 7.9 Hz), 3.66–3.63 (m, 1H), 3.41 (dd, 1H, J=9.5, 6.2 Hz), 2.76 (dd, 1H, J=16.7, 9.0 Hz), 2.50 (dd, 1H, J=16.7, 7.6 Hz), 2.34 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 140.8, 135.6, 130.5, 126.7, 126.5, 125.0, 54.1, 52.3, 40.2, 32.6, 27.7, 19.7; FT-IR (cm^{-1}): 1682 (C=O); HRMS (ESI) calcd for $C_{15}H_{22}NO$ $[M+H]^+$: 232.1701, found: 232.1693.

4.2.7. *N-tert*-Butyl-β-*m*-methylphenyl-γ-lactam (8f). Yield 74%. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25–7.19 (m, 1H), 7.07–6.96 (m, 3H), 3.83–3.79 (m, 1H), 3.44–3.37 (m, 2H), 2.73 (dd, 1H, J=15.8, 8.8 Hz), 2.58–2.34 (m, 1H), 2.34 (s, 3H), 1.43 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 142.5, 138.4, 128.7, 127.7, 127.5, 123.7, 54.1, 53.1, 40.6, 36.9, 27.7, 21.4; HRMS (ESI) calcd for $C_{15}H_{22}NO$ $[M+H]^+$: 232.1701, found: 232.1693.

4.2.8. *N-tert*-Butyl-β-benzyloxy-γ-lactam (8g). Yield 93%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.19 (m, 5H), 4.48 (d, 1H, J=11.8 Hz), 4.38 (d, 1H, J=11.8 Hz), 4.06–4.04 (m, 1H), 3.59 (dd, 1H, J=10.6, 6.4 Hz), 3.40 (dd, 1H, J=10.6, 3.3 Hz), 2.53 (dd, 1H, J=17.1, 6.9 Hz), 2.42 (dd, 1H, J=17.1, 4.0 Hz), 1.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 137.6, 128.5, 127.9, 127.7, 70.8, 70.4, 53.9, 52.1, 39.8, 27.7; HRMS (ESI) calcd for $C_{15}H_{22}NO_2$ $[M+H]^+$: 248.1651, found: 248.1647.

4.2.9. *N*-Benzyl-β-cyclohexyl-γ-lactam (10a). Yield 50%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.21 (m, 5H), 4.43 (s, 2H), 2.99 (s, 2H), 2.31 (s, 2H), 1.47–1.42 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0, 136.6, 128.6, 128.0, 127.5, 58.1, 46.4, 44.0, 36.9, 36.1, 25.5, 22.8; HRMS (ESI) calcd for $C_{16}H_{22}NO$ $[M+H]^+$: 244.1701, found: 244.1696.

4.2.10. *N*-Benzyl-β-benzyloxy-γ-lactam (10b). Yield 25%. Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.25 (m, 10H), 4.52–4.42 (m, 4H), 4.23–4.20 (m, 1H), 3.47 (dd, 1H, J=10.7, 6.1 Hz), 3.32 (dd, 1H, J=10.7, 2.9 Hz), 2.75–2.58 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 137.4, 136.1, 128.7, 128.5, 128.2, 128.0, 127.9, 127.7, 127.6, 70.9, 70.8, 52.7, 46.2, 38.2; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$: 282.1494, found: 282.1486.

4.2.11. *N*-Cyclohexylmethyl-2-aza-bicyclo[5,3,0]-decane-4,6,8-triene-1-one (11a). Yield 48% (white solid, easily decomposed in air). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50–6.44 (m, 2H), 6.20–6.14 (m, 2H), 5.29 (dd, 1H, J=9.8, 3.9 Hz), 4.19 (s, 2H), 3.23 (d, 2H, J=7.4 Hz), 3.09 (s, 1H), 1.76–1.61 (m, 6H), 1.25–1.17 (m, 3H), 1.05–0.97 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 130.3, 129.8, 129.5, 126.8, 120.9, 119.3, 51.7, 48.8, 46.4, 35.8, 30.7, 30.6, 26.3, 25.7; FT-IR (KBr, cm^{-1}): 3023, 2931, 2915, 2848, 1680, 1649, 1637, 1479, 1463, 1446, 1438, 1422, 1365, 1318, 1273, 1231, 940, 884, 817, 791, 719, 684.

4.2.12. *N*-Benzyloxyethyl-2-aza-bicyclo[5,3,0]-decane-4,6,8-triene-1-one (11b). Yield 39% (white solid, easily decomposed in air). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.26 (m, 5H), 6.50–6.46 (m, 2H), 6.15–6.12 (m, 2H), 5.26 (dd, 1H, J=9.5, 3.8 Hz), 4.51 (s, 2H), 4.33 (s, 2H), 3.68–3.59 (m, 4H), 3.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 137.8, 130.1, 129.8, 129.7, 128.6, 128.3, 128.1, 127.8, 127.6, 127.5, 126.8, 120.5, 119.1, 72.9, 68.3, 52.5, 46.1, 42.5; FT-IR (KBr, cm^{-1}): 3024, 2918, 2861, 1690, 1479, 1434, 1450, 1356, 1315, 1278, 1208, 1104, 1026, 738, 704.

4.3. General procedure for hydrolysis of γ-lactam (5, 8a, 8g)

A mixture of γ-lactam (0.85 mmol) in 25–28% HCl aqueous (6 mL) was heated at 90–120 °C for 18 h. After cooled to room temperature, the solution was extracted with diethyl ether (3×20 mL). The water was removed under reduced pressure to give the desired products (as the corresponding hydrochloride salt).

4.3.1. Gabapentin hydrochloride (1). Yield 84% (white solid). ^{1}H NMR (300 MHz, D_2O) δ 3.00 (s, 2H), 2.43 (s, 2H), 1.40–1.30 (m, 10H); ^{13}C NMR (75 MHz, D_2O) δ 176.9, 47.5, 40.7, 35.5, 33.6, 25.9, 21.4.

4.3.2. (±)-Baclofen hydrochloride (2). Yield 95% (white solid). ^{1}H NMR (300 MHz, D_2O) δ 7.45 (d, 2H, J=8.4 Hz), 7.35 (d, 2H, J=8.5 Hz), 3.49–3.25 (m, 3H), 2.86 (dd, 1H, J=16.1, 5.9 Hz), 2.74 (dd, 1H, J=16.1, 8.6 Hz); ^{13}C NMR (75 MHz, D_2O) δ 177.8, 139.7, 136.0, 132.1, 131.9, 46.3, 42.0, 40.8.

4.3.3. (±)-GABOB hydrochloride (3). Yield 95% (white solid). ^{1}H NMR (300 MHz, D_2O) δ 4.35–4.26 (m, 1H), 3.22 (dd, 1H, J=10.8, 2.3 Hz), 3.05–2.98 (m, 1H), 2.71 (dd, 1H, J=16.1, 4.6 Hz), 2.59 (dd, 1H, J=16.1, 8.2 Hz); ^{13}C NMR (75 MHz, D_2O) δ 174.3, 64.0, 43.5, 38.9.

4.3.4. (±)-*N*-Boc-GABOB (13) and *N*-Boc-α,β-unsaturated γ-amino butyric acid (*N*-Boc-12). A mixture of γ-lactam **8g** (1.7 g, 6.8 mmol) in 25% aqueous HCl (24 mL) was heated in an oil bath (120 °C) for 18 h. After cooling to room temperature, the solution was extracted with diethyl ether (3×20 mL). The water was removed under reduced pressure. The residue was dissolved in water (30 mL). To the solution, potassium carbonate (1.5 g, 108.5 mmol) and di-*tert*-butyl dicarbonate (1.5 g, 6.8 mmol) were added in sequence. The resulting mixture was stirred at room temperature for 12 h. After being acided by saturated sodium sulfate solution to pH 3–4 in ice-bath, the mixture was extracted with diethyl ether (3×20 mL). The combined organic layer was dried over sodium sulfate, filtered and concentrated with a rotary evaporator. The residue was purified by silica gel column chromatography (petrol ether/ethyl acetate, 3:1 v/v) to give (±)-*N*-Boc-GABOB and *N*-Boc-α,β-unsaturated γ-amino butyric acid.

(±)-N-Boc-GABOB (**13**). 1.01 g, 67% yield, white solid, mp: 97.5–98.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.29 (s, 1H), 4.16–4.09 (m, 1H), 3.44–3.23 (m, 1H), 3.20–3.11 (m, 1H), 2.54–2.46 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 157.1, 80.2, 67.8, 45.5, 38.4, 28.3; MS (EI): 219 [M^+].

N-Boc-α,β-unsaturated γ-amino butyric acid (*N*-Boc-**12**). 75 mg, 5% yield, white solid, mp: 132.5–133.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05–6.97 (m, 1H), 5.98–5.92 (m, 1H), 4.73 (s, 1H), 3.95 (s, 2H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5, 155.6, 147.4, 120.5, 80.0, 41.4, 28.2.

Acknowledgements

We acknowledge the financial support from the Chinese Academy of Sciences and the National Science Foundation of China (Grant No. 20202011).

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