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A New Synthesis of 4, 4-Diaryl/Diheteroaryl-3-butenyl Derivatives of Nipecotic Acids as GABA Transporter Inhibitors

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Abstract: A new method for the synthesis of 4, 4-diaryl/diheteroaryl-3-butenyl derivatives of nipecotic acid as GABA transporter inhibitors is described. The key intermediates 4-tosyl-1, 1-diaryl/diheteroaryl-1-butene **10a-d** were synthesized by Wittig reaction**,** and followed by alkylation with (*R*)-3-piperidinecarboxylate. The resulting N-cycloalkylated amino acid esters **11a-d** were saponified and then acidified to get the target compounds **1a-d**. The preliminary bioassays showed that **1a-d** exhibited excellent inhibition of [^{3}H]-GABA uptake in *vitro* of culture cells.

Keywords: Tiagabine, nipecotic acid, derivatives, synthesis, GABA transporter inhibitor.

γ-Aminobutyric acid (GABA) is recognized as the principal brain inhibitory neurotransmitter. GABA uptake from the synaptic cleft is one of the important mechanisms in the regulation of GABA activity. Inhibition of the uptake of GABA by potent and selective inhibitors of the GABA transporter such as **1a** can enhance GABA activity. This property is considered to be useful for the treatment of epilepsy or psychiatric disorders[1-4].

1a, named as tiagabine, (*R*)-1-[4, 4-bis (3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylic acid hydrochloride, is 4, 4-diheteroaryl-3-butenyl derivative of nipecotic acid. Although the synthesis of **1a** and its analogues have been reported[5], there are still rooms for improvement to find a more practical and general way for the synthesis of **1a** and its analogues. Herein, we wish to report a new approach for the synthesis of **1a** and its derivatives.

As shown in **Scheme 1**, the key intermediate 4-chloro-1, 1-diaryl/diheteroaryl-1-butene **6a-d** could be prepared by methylenyl cyclopropane ring-opening of **5a-d** in the presence of Lewis acid[6], and **5a-d** could be synthesized by the treatment of ketones **2a-d** with the Wittig reagent **4,** generated from 3-bromopropyltriphenyl phosphonium bromide **3** with treatment of potassium *tert*-butoxide in refluxing tetrahydrofuran[7]. However**,** under such condition**,** the yields of **5a-d** were low due to the formation of by-products of the possible self-condensation of **4**.

In seeking ways to make the Wittig reaction successful in high yields, another

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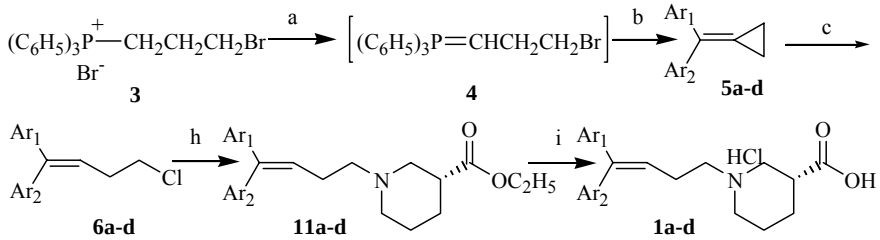
Wittig reagent **8,** which was prepared from 3-*O*-tetrahydropyranylpropyltriphenylphosphonium bromide **7** with potassium *tert*-butoxide in refluxing benzene, was tried to treat with ketones **2a-d**. To our delight, the products **9a-d** was resulted in good yields[8]. **9a-d** were then converted easily to the corresponding tosylates **10a-d** in good yields (see **Scheme 2**). The protection of hydroxyl moiety by forming tetrahydropyrany could be the reason to minimize the formation of by-products.

Then, the intermediates **10a-d** were reacted with ethyl (*R*)-3-piperidinecarboxylate to afford the esters **11a-d**. Finally, upon saponification followed by acidification yielded the target compounds **1a-d** as their hydrochloride salts in crystalline forms.

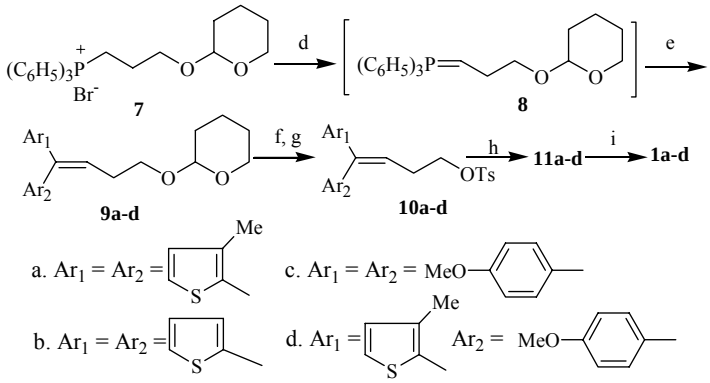
The overall yields of **1a** by using this method is up to 42% while the overall yields of **1a** in the **Scheme 1** was 14%. Hence, the yields of the corresponding 4, 4-diaryl/diheteroaryl-3-butenyl derivatives of nipecotic acid **1b-d** were 40%, 43% and 38% for **1b**, **1c** and **1d** according to the route shown in **Scheme 2**, respectively.

The IC_{50} values of the synthetic compounds **1a-d** and **11a-d** *in vitro* test for [^{3}H]-GABA uptake inhibitors were determined[9]. The preliminary biological test showed that the target compounds **1a-d** exhibited excellent inhibitions of [^{3}H]-GABA uptake in culture cell, especially **1a** and **1b**. However, **1c** or **1d** tends to be weaker than

Scheme 1



Scheme 2



Reagents and conditions: a. *t*-BuOK, THF, reflux, 2 h; b. Ar_1COAr_2 **2a-d**, THF, 65˚C, 3 h; c. 4 mol/L HCl in dioxane, 120˚C, 10 min; d. *t*-BuOK, benzene, reflux, 1 h; e. Ar_1COAr_2 **2a-d**, benzene, reflux, 2 h, 84%-87%; f. 5% HCl, THF, r.t. 6 h; g. pyridine, TsCl, $CHCl_3$, 40-50˚C, 48 h, 78%-84% (for f, g steps); h. ethyl (R) 3-piperidinecarboxylate, KI, K_2CO_3, acetone, r.t. 48 h, 71-78%; i. (1) 12 mol/L NaOH, C_2H_5OH, r.t. 5 h, (2) 2 mol/L HCl, 72-80%.

1a or **1b**. It is likely to be due to replace the more polar thienyl group with phenyl group. Another observation is the corresponding acid esters **11a-d** are almost inactive. It appears that the polar diheteroaryl substituted group and nipecotic free acid play the very important role for the inhibitory activities. The computer assisted QSAR study is going on and the results will be published later.

The yields, melting points, $[\alpha]_D^{25}$ and IC_{50} of compounds **11a-d** and **1a-d** were listed in **Table 1**.

Table 1 The yields, melting point, $[\alpha]_D^{25}$ and IC_{50} of compounds **11a-d** and **1a-d**[*]

Compd.	Ar_1	Ar_2	Yield (%)	Mp (^oC)	$[\alpha]_D^{25}$	IC_{50} (μmol)
11a	3-methyl-2-thienyl	3-methyl-2-thienyl	76		-26.0 (c 1.00, EtOH)[a]	170
11b	2-thienyl	2-thienyl	70		-10.1(c 1.00, CH_3OH)	266
11c	4-methoxyphenyl	4-methoxyphenyl	74		-3.6 (c 1.00, CH_3OH)	(–)
11d	3-methyl-2-thienyl	4-methoxyphenyl	65		-9.5 (c 1.00, CH_3OH)	(–)
1a	3-methyl-2-thienyl	3-methyl-2-thienyl	90	185~186[b]	-9.9 (c 1.00, H_2O)[b]	0.44
1b	2-thienyl	2-thienyl	92	181~182	-9.0 (c 1.00, CH_3OH)	0.40
1c	4-methoxyphenyl	4-methoxyphenyl	94	94~95	-4.1 (c 1.00, CH_3OH)	6.99
1d	3-methyl-2-thienyl	4-methoxyphenyl	85	99~101	-6.7 (c 1.00, CH_3OH)	1.13

[*]: compounds **11a-d** were oil. *a.* **11a**: $[\alpha]_D^{25}$ -25.5 (c 1.00, EtOH) [lit.,5]; *b.* **1a**: mp. 183.5~185.5°C, $[\alpha]_D^{25}$ -10.0 (c 1.00, H_2O) [lit.,5].

General procedures for the preparation of the target compounds **11a-d**:

3-*O*-Tetrahydropyranylpropyltriphenylphosphoniumbromide **7** (9.90 mmol), potassium *tert*-butoxide (10.00 mmol) were mixed in dry benzene (50 mL) and the mixture was refluxed. Diaryl ketones **2a-d** (7.60 mmol) in benzene (20 mL) were added and then kept in reflux. According to the general disposal procedure, **9a-d** were obtained (84%-87%) as oil.

The diaryl/dihetroaryl substituted **9a-d** (7.3 mmol) were dissolved in tetrahydrofuran (60 mL), 2 mol/L hydrogen chloride (45 mL) was added and stirred. The solvent was removed, the residue was dissolved in dry chloroform (60 mL), and treated with pyridine (43.8 mmol), *p*-toluenesulfonyl chloride (29.2 mmol), stirred at 40-50°C. According to the general disposal procedure, **10a-d** were provided (78%-84%) as oil.

The diaryl/dihetroaryl substituted **10a-d** (10.0 mmol) were dissolved in acetone (50 mL), ethyl (*R*)-3-piperidinecarboxylate (10.0 mmol), potassium iodide (1.0 mmol), and potassium carbonate (10.0 mmol) were added and stirred at room temperature. According to the general disposal procedure, **11a-d** were provided (71-78%) as a gum.

Acknowledgments

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9. The [^{3}H]-GABA uptake inhibition bioassays *in vitro* were carried out by Mr. Linfend Xu and professor Li He Guo. The results will be published elsewhere in due course.
10. Dates for compounds **11a-d**: **11a**: ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm) : 1.21(t, 3H, J=7.2Hz, $COOCH_2CH_3$), 1.26-1.72(m, 3H), 1.93(m, 2H), 2.02 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.09-2.17 (m, 1H), 2.34 (q, 2H, J=6.9Hz, C_2-H), 2.54 (m, 3H), 2.73(m, 1H), 2.96(m, 1H), 4.07-4.15 (q, 2H, J=7.2Hz, $COOCH_2$-), 6.03 (t, 1H, J=7.2Hz, C_3-H), 6.76(d, 1H, J=4.8Hz, ArH), 6.84 (d, 1H, J=4.8Hz, ArH), 7.06 (d, 1H, J=4.5Hz, ArH), 7.22 (d, 1H, J=4.8Hz, ArH); EIMS(*m/z*, %): 403(M^+), 170(100), 142; HRMS(MAIDI): Calcd. for $C_{22}H_{29}NO_2S_2$+H: 404.1729, Found 404.17125. **11b**: ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 1.22(m, 3H, COO-CH_2CH_3), 1.39-1.56 (m, 2H),1.65-1.7(m, 1H),1.89-1.98 (m, 2H), 2.38-2.56(m, 6H), 2.69-2.96 (m, 2H), 4.07-4.14 (q, 2H, J=7.2Hz, $COOCH_2$-), 6.1(t, 1H, J=7.5Hz, C_3-H), 6.79(m, 1H, ArH), 6.90(m, 1H, ArH), 6.99 (m, 1H, ArH), 7.05(m, 1H, ArH), 7.12 (m, 1H, ArH), 7.33 (m, 1H, ArH); ESI-MS: 376[M+H]$^+$; HRMS: Calcd. for $C_{20}H_{25}NO_2S_2$+H: 376.1397040, Found 376.1399469. **11c**: ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 1.26 (m, 3H, $COOCH_2CH_3$), 1.38-1.56 (m, 3H), 1.98 (m, 2H), 2.15 (m, 1H), 2.34 (q, 2H, J=7.5Hz, C_2-H), 2.49 (m, 2H, C_1-H), 2.54 (m, 1H), 2.74 (m, 1H), 2.97 (m, 1H), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.08-4.15 (q, 2H, J=7.2Hz, $COOCH_2$-), 5.94 (t, 1H, J=7.5Hz, C_3-H), 6.81 (m, 2H, ArH), 6.91 (m, 2H, ArH), 7.07-7.17 (m, 4H, ArH); EIMS(*m/z*, %): 423 (M^+), 170 (100), 142; HRMS (MALDI): Calcd. for $C_{26}H_{34}NO_4$+H: 424.2464, Found 424.24824. **11d**: ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 1.25 (m, 3H, $COOCH_2CH_3$), 1.28-1.71 (m, 4H), 1.93-1.99 (m, 2H), 2.00 (s, 3H, CH_3), 2.15-2.20 (m, 1H), 2.23-2.30 (q, 2H, J=7.2Hz, C_2-H), 2.40-2.56 (m, 2H, C_1-H), 2.70-2.73 (m, 1H), 2.93-2.96 (m, 1H), 3.78 (s, 3H, OCH_3), 4.07-4.14 (q, 2H, J=7.2Hz, $COOCH_2$-), 5.94-5.98, 6.14-6.19 (2t, 1H, J=7.2Hz, C_3-H), 6.74-6.89 (m, 3H, ArH), 7.14-7.35 (m, 3H, ArH); EIMS(*m/z*, %): 413 (M^+), 170 (100), 142; HRMS(EI): Calcd. for $C_{24}H_{31}NO_3S$: 413.2018, Found 413.2019.
11. Dates for compounds **1a-d**: **1a**: ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 1.29-2.20 (m, 4H), 2.40 (s, 3H), 2.42 (s, 3H), 2.64-3.01 (m, 5H), 3.22 (m, 2H), 3.50 (m, 1H), 3.67 (m, 1H), 6.00 (m, 1H), 6.59-6.65 (m, 2H), 6.77-6.85 (m, 2H); ESI-MS: 376[M-Cl]$^+$; HRMS(ESI): Calcd. for $C_{20}H_{26}ClNO_2S_2$-HCl+H+Na: 398.1214, Found 398.1218. **1b**: ^{1}H-NMR (300MHz, CD_3OD, δ ppm): 1.56-2.17 (m, 5H), 2.65-2.73 (q, 2H, J=7.5Hz, C_2-H), 2.86-3.03 (m, 2H), 3.22-3.28 (m, 2H), 3.58 (m, 1H), 3.63 (m, 1H), 6.18 (t, 1H, J=7.2Hz, C_3-H), 6.86-6.96 (m, 2H, ArH), 7.09-7.15 (m, 2H, ArH), 7.30-7.32 (m, 1H, ArH), 7.53-7.55 (m, 1H, ArH); ESI-MS: 348 [M-Cl]$^+$; HRMS(ESI): Calcd. for $C_{18}H_{22}ClNO_2S_2$-HCl+H: 348.1096, Found 348.1086. **1c**:^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 1.16-1.37 (m, 2H), 1.80 (m, 1H), 2.00-2.10 (m, 2H), 2.14-2.43 (m, 3H), 2.56-3.28 (m, 3H), 3.40-3.53 (m, 2H), 3.70 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 5.82 (t, 1H, J=7.2Hz, C_3-H), 6.73 (m, 2H, ArH), 6.82 (m, 2H, ArH), 6.99-7.20 (m, 4H, ArH); ESI-MS: 396 [M-Cl]$^+$; HRMS(ESI): Calcd. for $C_{24}H_{30}ClNO_4$-HCl+H: 396.2165, Found 396.2169. **1d**: ^{1}H-NMR (300MHz, $CDCl_3$, δ ppm): 1.86-1.94 (m, 2H), 1.97 (s, 3H, CH_3), 2.18-2.29 (m, 2H), 2.50-2.54 (m, 1H), 2.60-2.72 (m, 3H), 3.03-3.42 (m, 4H), 3.65-3.69 (m, 1H), 3.78 (s, 3H, OCH_3), 6.13-6.18 (t, 1H, J=7.2Hz, C_3-H), 6.75-6.92 (m, 3H, ArH), 7.06-7.26 (m, 3H, ArH); ESI-MS: 386[M-Cl]$^+$; HRMS(ESI): Calcd. for $C_{22}H_{28}ClNO_3S$-HCl + H: 386.1777, Found 386.1784.

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