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Double π-Bond Isomerization/Friedel–Crafts Reaction Involving γ-Amidocronates: Access to γ-Aryl/Heteroaryl GABA Scaffolds and Dihydropyrido[1,2-*a*]indoles

Anvita Srivastava[a] and Sampak Samanta*[a]

Abstract: A series of pharmacologically attractive γ-indolyl/furyl/aryl-substituted γ-amino esters/γ-aminoketones were obtained in good to high combined yields by π-bond isomerization of *N*-protected γ-aminocrotonates/γ-aminocrotonophenones in the presence of triethylamine, followed by tandem Friedel–Crafts alkylation involving several indole/furan/arene derivatives and the resultant *N*-protected enamines at room temperature by using $B(C_6F_5)_3$ (5 mol-%) as an efficient Lewis acid catalyst. Moreover, the easy synthesis of the important class of 8,9-dihydropyrido[1,2-*a*]indole scaffolds was realized by this unique procedure. Thus, a simple, convenient, and metal-free-based protocol may provide an alternative powerful synthetic route for heteroarylation/arylation at the γ positions of GABA derivatives in a practical manner.

Introduction

The development of an efficient, atom-economical, and metal-free-based new synthetic technique for straightforward access to the important class of γ-aminobutyric acid (GABA) analogues is unanimously one of the most challenging research areas in synthetic, bioorganic, and medicinal chemistry because this nonprotein amino acid and its derivatives are largely found in a variety of natural products and active pharmaceuticals (Figure 1).[1] Apart from its valuable applications as a reactive intermediate, GABA also plays a critical role as a major inhibitory neurotransmitter in the central nervous system of mammals, and its critical imbalance causes several neurological and psychiatric disorders including Parkinson's disease, Huntington's disease, epilepsy, anxiety, and so on.[1,2] In view of the great applications of GABAergic drugs, a large number of synthetic strategies have been developed to access α- and β-substituted GABA analogues.[3] On the contrary, access to γ-substituted GABA derivatives has seen little attention so far.[4] For instance, diastereoselective reduction of in situ generated 4-(sulfinylimino)butanoate by using a stoichiometric amount of L-Selectride was realized by Reddy et al. (Scheme 1, a).[4a] After that, in 2013, the scandium(III) trifluoromethanesulfonate [$Sc(OTf)_3$]-catalyzed Friedel–Crafts (FC) alkylation of indoles with aminocyclopropane derivatives was reported by the Waser group (Scheme 1, b).[4b] In 2015, Ramachandran et al. also synthesized γ-aryl-substituted GABA derivatives in poor to good yields through Rh-catalyzed arylboronic acid addition to optically active 4-(sulfinylimino)butanoate.[4c] Even with this progress, there is still a need for metal-free, catalytic, high-yielding, general methods towards the preparation of γ-aryl/heteroaryl-substituted GABA derivatives. On the other hand, the FC reaction of electron-rich arenes/heteroarenes with *N*-protected imines or enamines (surrogates of imines) catalyzed by several Lewis acids and Brønsted acids is one of the most reliable methods for the construction of aryl/heteroaryl-substituted methanamine derivatives.[5]

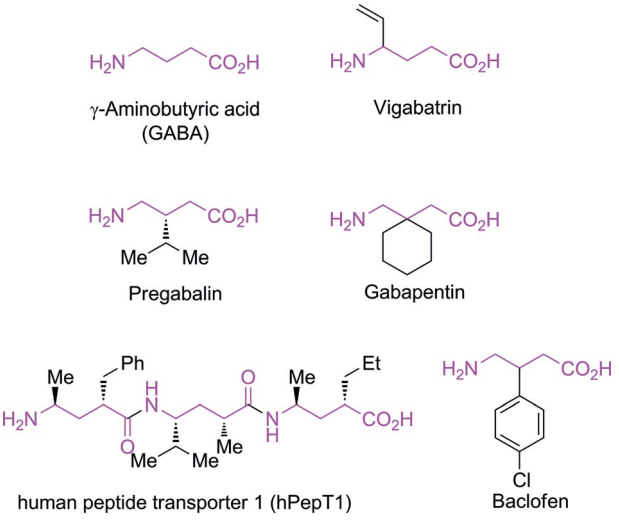

Figure 1. Pharmacologically active GABAergic drugs.

However, the direct synthesis of alkyl-substituted aldimines/enamines from the corresponding aldehydes and their subsequent isolation remain complicated issues in organic synthesis. To overcome these difficulties, *N*-protected allylamine was efficiently employed as an alternative imine source in a FC reaction with several activated arenes through a one-pot tandem double π-bond isomerization reaction by using a Ru complex/Brønsted

[a] *Department of Chemistry, Indian Institute of Technology Indore, Indore, Simrol 452020, Madhya Pradesh, India*
E-mail: sampaks@iiti.ac.in
http://iiti.ac.in/people/~sampaks/

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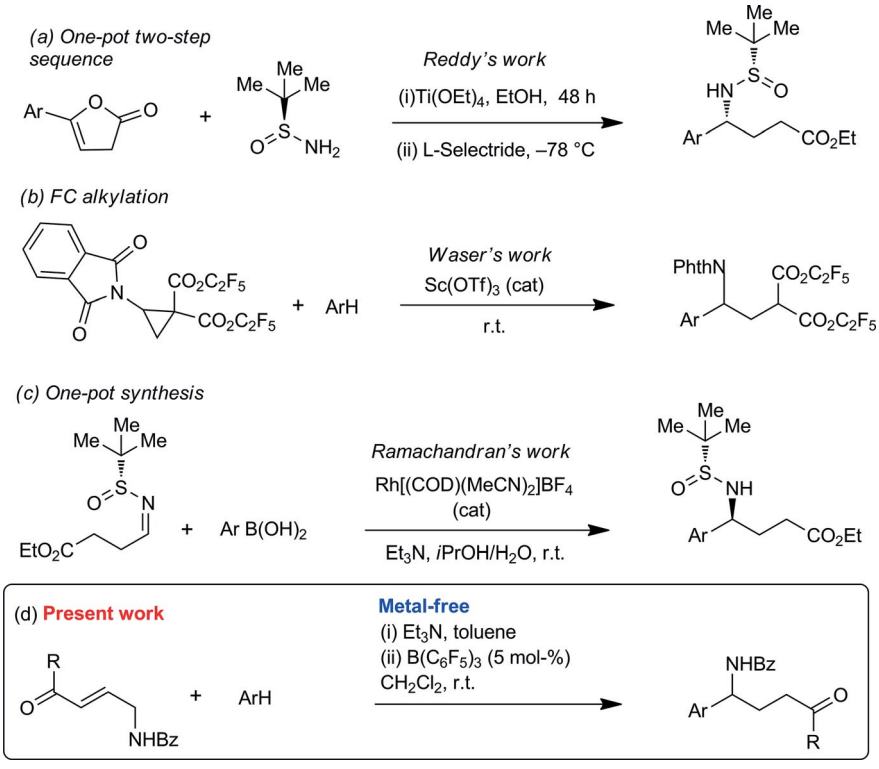


Scheme 1. Various approaches to γ-aryl-substituted GABA derivatives (Phth = phthaloyl, cod = 1,5-cyclooctadiene, Bz = benzoyl).

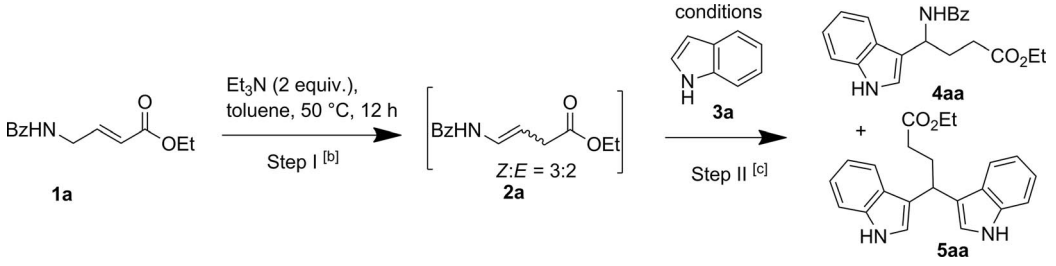
acid binary system.[6] Besides the success of metal complexes,[6,7] simple bases such as NaH and KO*t*Bu[8] have also been effectively used to promote the π-bond shifting process from the β,γ positions to the α,β positions of *N*-protected allyl derivatives. In view of these facts, we thought that γ-aryl/heteroaryl-substituted GABA derivatives could be obtained from γ-amidocrotonates through π-bond isomerization by using a base, followed by FC alkylation of arenes/heteroarenes with the generated enamines catalyzed by a Lewis acid/Brønsted acid.

As part of our research focused on the development of new synthetic techniques for the preparation of indole derivatives,[9] we report herein a simple protocol for the synthesis of a wide range of γ-indolyl/furyl/aryl-substituted γ-amino esters/ketones by sequential π-bond isomerization of *N*-protected γ-aminocrotonates/aminocrotonophenones in the presence of triethylamine, followed by tandem π-bond isomerization/FC reaction of the resultant *N*-protected enamines with heteroarenes/arenes by using $B(C_6F_5)_3$ as a well-known Lewis acid catalyst.[10]

Results and Discussion

To optimize the reaction conditions, we began an isomerization reaction of *N*-Bz-γ-aminocrotonate **1a** in toluene at room temperature for 24 h by using Et_3N (2.0 equiv.) as a Lewis base, followed by removal of the base [*N*-Bz protected enamine **2a**, *Z*/*E* = 3:2, 63 % conversion by ^1H NMR spectroscopy] and subsequent addition of indole (**3a**) and $B(C_6F_3)_3$ (5 mol-%) in toluene at room temperature to provide γ-indol-3-yl-GABA derivative **4aa** in 51 % yield along with a trace amount of bis-indolylmethane **5aa** (5 %) within 18 h (Table 1, entry 1). Notably, both the *Z* and *E* geometrical isomers of enamine **2a** were isolable in pure forms through column chromatography. However, the obtained yield was considerably lower than expected, owing to the instability of this acyclic enamine during silica gel column chromatography. Very interestingly, if the isomerization step (i.e., step I) was conducted at 50 °C for 12 h (**1a** was fully isomerized into **2a**, for details see the Supporting Information), followed by tandem FC reaction (step II;[11] Table 1, entry 2), desired product **4aa** was obtained in high overall yield (76 %, two steps). Next, we focused on standardization of step II by performing the FC reaction in common organic solvents (e.g., THF, DMF, MeCN, EtOH, CH_2Cl_2, and $CHCl_3$) at room temperature for 18 h in the presence of $B(C_6F_5)_3$. Among the solvents studied (Table 1, entries 3–8), toluene and halogenated solvents such as $CHCl_3$ (Table 1, entry 7) and CH_2Cl_2 (Table 1, entry 8) were suitable media for this reaction, and they led to desired product **4aa** in high yields of 76, 75, and 80 % respectively. Considering the lower boiling point of CH_2Cl_2, it was chosen as the best solvent for this tandem FC alkylation reaction (Table 1, entry 8). To evaluate the best catalyst for this FC reaction, several well-known Brønsted acids (Table 1, entries 9–13) and Lewis acids (Table 1, entries 14–16) catalysts were tested in CH_2Cl_2 at room temperature. Among them, trifluoroacetic acid (TFA), trichloroacetic acid (TCA), 10-camphorsulfonic acid (CSA), 4-toluenesulfonic acid (PTSA), and $In(OTf)_3$ were able to promote this reaction effectively; they gave moderate to good yields (55–71 %; Table 1, entries 9–14) of GABA analogue **4aa** along with

Table 1. Optimization of the reaction conditions.[a]

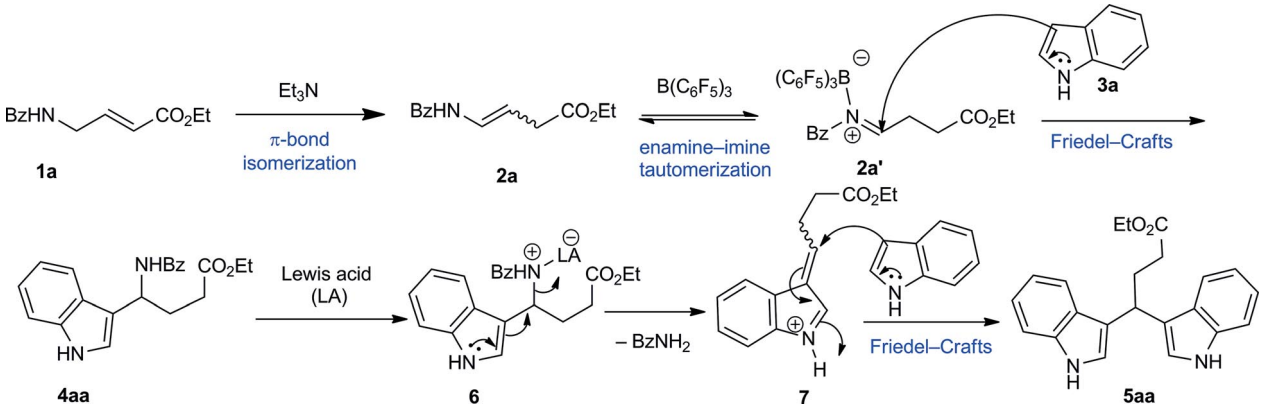


Entry	Conditions (Step II)[c]	Yield[d] [%]	
		4aa	**5aa**
1[b]	$B(C_6F_5)_3$, toluene, r.t., 18 h	51	<5
2	$B(C_6F_5)_3$, toluene, r.t., 18 h	76	9
3	$B(C_6F_5)_3$, THF, r.t., 18 h	17	8
4	$B(C_6F_5)_3$, DMF, r.t., 18 h	19	7
5	$B(C_6F_5)_3$, EtOH, r.t., 18 h	13	<5
6	$B(C_6F_5)_3$, MeCN, r.t., 18 h	57	11
7	$B(C_6F_5)_3$, $CHCl_3$, r.t., 18 h	75	14
8	$B(C_6F_5)_3$, CH_2Cl_2, r.t., 18 h	80	9
9	$PhCO_2H$, CH_2Cl_2, r.t., 18 h	<5	–
10	TFA, CH_2Cl_2, r.t., 18 h	64	15
11	TCA, CH_2Cl_2, r.t., 18 h	67	10
12	(±)-CSA, CH_2Cl_2, r.t., 18 h	70	14
13	PTSA, CH_2Cl_2, r.t., 18 h	71	15
14	$In(OTf)_3$, CH_2Cl_2, r.t., 18 h	55	17
15	$Yb(OTf)_3$, CH_2Cl_2, r.t., 18 h	5	–
16	$Gd(OTf)_3$, CH_2Cl_2, r.t., 18 h	7	–

[a] Unless otherwise noted, step I was performed with compound **1a** (0.2 mmol) and Et_3N (2.0 equiv.) in dry toluene (0.2 mL) at 50 °C for 12 h under an argon atmosphere. [b] Step I was performed with compound **1a** (0.2 mmol) and Et_3N (2.0 equiv.) in dry toluene (0.2 mL) at room temperature for 24 h under an argon atmosphere. [c] After removal of Et_3N, a mixture of crude enamine **2a**, indole (**3a**, 0.24 mmol), and catalyst (5.0 mol-%) was stirred in the specified dry solvent (0.2 mL) at room temperature under an atmosphere of argon. [d] Combined yield (two steps) of isolated product after column chromatography.

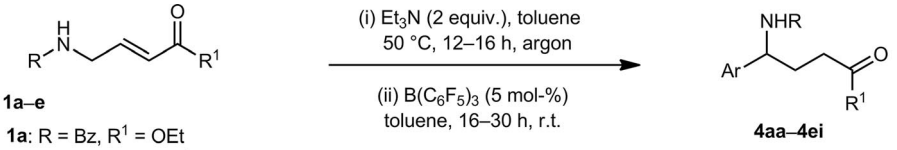
10–17 % yields of **5aa**. Thus, $B(C_6F_5)_3$ was chosen as the best catalyst for further experiments (Table 1, entry 8).

Considering the above experimental results collectively, a possible mechanism for the formation of both FC adducts **4aa** and **5aa** is shown in Scheme 2. In the first step, the π bond of *N*-Bz-protected **1a** is shifted from the α,β positions to the β,γ positions through an isomerization process by using triethylamine to produce enamine **2a**. The latter isomerizes to iminium ion **2a′** under 3the influence of $B(C_6F_5)_3$ as a Lewis acid [LA]. Subsequently, indole (**3a**) attacks **2a′** to give FC adduct **4aa**. On the other hand, $B(C_6F_5)_3$ may further coordinate to the amide N atom of **4aa** to form Lewis acid complex **6**, which undergoes elimination of $PhCONH_2$ by pushing a lone pair of electrons from the ring N atom to generate vinyl iminium ion **7**. Finally,



Scheme 2. Possible mechanism for the formation of **4aa** and **5aa**.

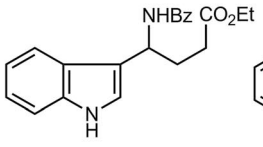
Table 2. Two-step synthesis of γ-indolyl-substituted γ-amino esters/ketones **4aa**–**ei**.

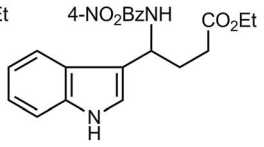


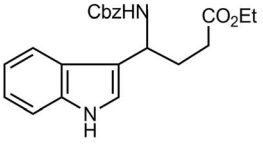
1a–e

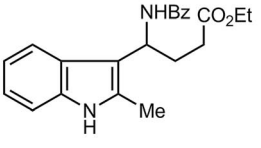
1a: R = Bz, R^1 = OEt
1b: R = 4-NO_2-Bz, R^1 = OEt
1c: R = Cbz, R^1 = OEt
1d: R = Bz, R^1 = O*t*Bu
1e: R = Bz, R^1 = Ph

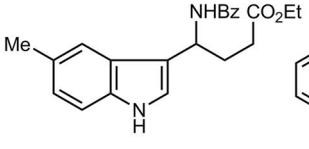
4aa–4ei

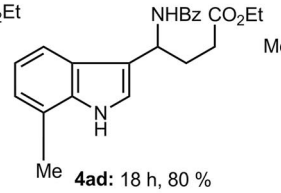

4aa: 18 h, 80 %

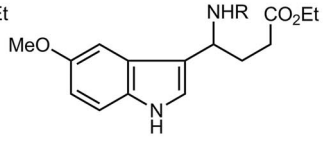

4ba: 18 h, 78 %

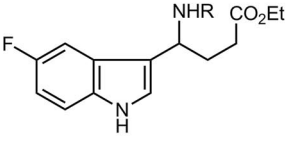

4ca: 18 h, 75 %

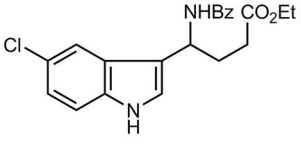

4ab: 18 h, 77 %

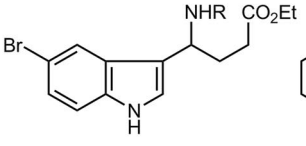

4ac: 18 h, 82 %

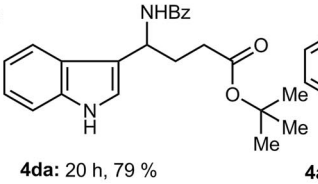

4ad: 18 h, 80 %

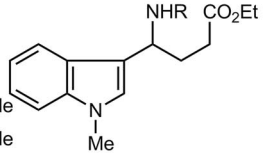

4ae: 18 h, 84 %

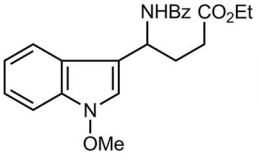

4af: R = Bz, 28 h, 73 %
4bf: R = 4-NO_2Bz, 28 h, 70 %

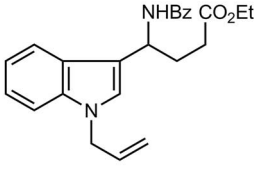

4ag: 26 h, 74 %

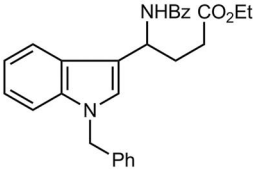

4ah: R = Bz, 26 h, 26 h, 75 %
4bh: R = 4-NO_2Bz, 26 h, 69 %

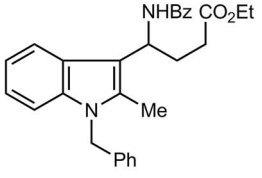

4da: 20 h, 79 %

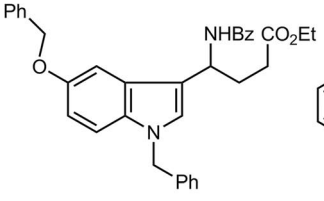

4ai: R = Bz, 19 h, 83 %
4bi: R = 4-NO_2Bz, 20 h, 80 %

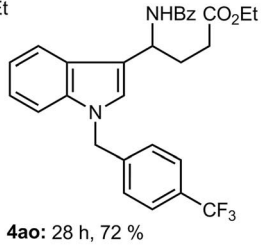

4aj: 16 h, 84 %

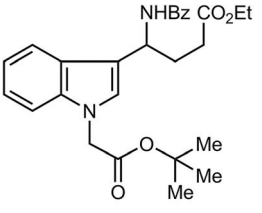

4ak: 20 h, 78 %

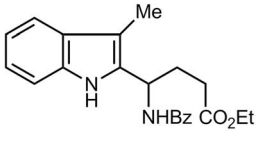

4al: 24 h, 74 %

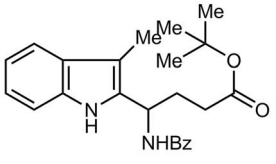

4am: 24 h, 73 %

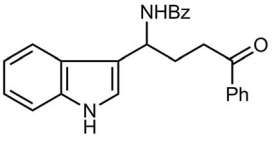

4an: 28 h, 70 %


4ao: 28 h, 72 %


4ap: 26 h, 71 %


4aq: 30 h, 77 %


4dq: 30 h, 76 %


4ea: 16 h, 85 %

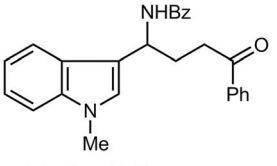
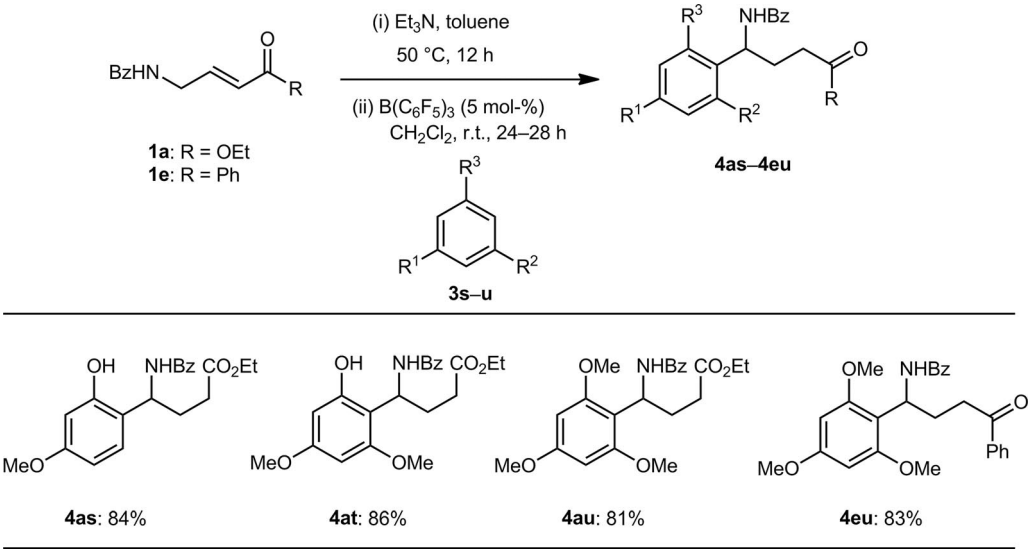

4ei: 18 h, 83 %

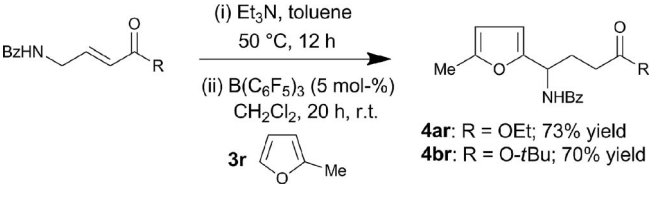
Table 3. Synthesis of γ-aryl-substituted amino ester/ketones **4as**–**4eu**.



bis-indolyl adduct **5aa** is formed through FC alkylation of indole with intermediate **7**.

Next, we applied the above optimal reaction conditions to examine the general trends of this sequence process by performing the FC alkylation reaction of a variety of structurally and electronically diverse indoles with *N*-protected enamines **2a–e** (generated in situ from corresponding *N*-protected γ-aminocrotonates/γ-aminocrotonophenones **1a–e**) by using a catalytic amount of $B(C_6F_5)_3$ as a Lewis acid catalyst. Typical results are systematically organized in Table 2. The results clearly demonstrate that reactions of *N*-unprotected indoles having a variety of substituents, including Me, OMe, F, Cl, and Br, at the C2, C5, and C7 positions ran easily with several *N*-Bz/4-nitrobenzoyl (4-NO_2Bz)/benzyloxycarbonyl (Cbz)-protected enamines **2a–d** derived from corresponding *N*-protected γ-aminocrotonates **1a–d** under the present conditions, which led to new functionalized γ-indol-3-yl-substituted GABA analogues **4aa**–**da** in good to high combined yields (69–84 %, two steps). During the course of the reactions, we observed that reactions of indoles with electron-rich substituents ran slightly faster than those performed with indoles with electron-poor substituents (18–20 h vs. 26–28 h). Next, several *N*-protected indoles were used as FC donors in the present catalytic system. The results show that Me, OMe, and allyl protecting groups did not hamper the reactivity of the indoles towards enamines **2a** and **2b**, which afforded corresponding GABA derivatives **4ai**–**ak** in high overall chemical yields (78–84 %) within 16–20 h. However, indoles with benzyl/4-trifluoromethylbenzyl/*tert*-butyl acetate protecting groups also reacted with enamine **2a** by this procedure but delivered the targeted products in slightly lower yields over reaction times that were longer than those with other protecting groups. To our satisfaction, 3-methylindole was employed as a challenging nucleophile in the tandem FC reaction with enamines **2a** and **2d** in our present catalytic system, and it furnished 3-methyl-2-indolyl-substituted GABA derivatives **4aq** and **4dq** in high yields (76–77 %). Very interestingly, the chemoselective Friedel–Crafts alkylation reaction was investigated by combining indoles **3a** and **3i** with *N*-Bz-protected enamine **2e** possessing two reactive groups such as C=O and enamine (CH=CH–NH–, tautomeric form of imine C=N). Gratifyingly, the indoles attacked exclusively at the imine bond instead of the C=O group in the present catalytic system, which resulted in FC adducts **4ea** and **4ei** in yields of 85 and 83 %, respectively. Notably, several chemically sensitive functional groups, namely, CO_2Et, CO_2*t*Bu, NHBz, 4-NO_2BzNH, Cbz, N-OMe, OMe, O-benzyl (Bn), NBn, OH, F, Cl, Br, allyl, and furyl were unaffected under our present conditions, and this provides additional scope for further modification of the above functional groups.

Towards expanding the substrate scope, 2-methylfuran (**3r**) was employed as a nucleophile in Friedel–Crafts reactions with *N*-Bz enamines **2a** and **2d** under this sequence process. Satisfactorily, after 20 h, corresponding 2-furyl-functionalized GABA derivatives **4ar** and **4br** were obtained in good yields (70–73 %, Scheme 3).

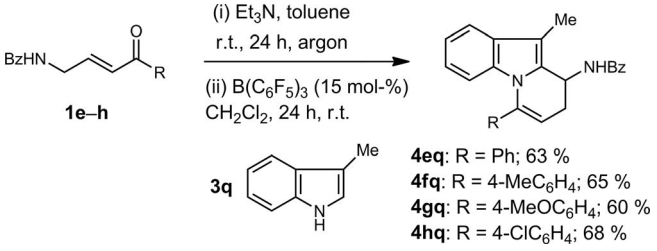


Scheme 3. γ-(2-Furyl)-substituted GABA analogues **4ar** and **4br**.

After successfully employing several heteroarenes as suitable FC donors, we decided to use several simple electron-rich arenes, namely, 3-cresol (**3r**), 2,5-dimethoxyphenol (**3s**), and 1,3,5-trimethoxybenzene (**3t**) as nucleophiles. By this procedure, the FC reactions between phenolic derivatives **3r**–**s** and *N*-Bz-protected enamine **2a** (in situ generated from **1a**) took place exclusively at the *ortho* position (i.e., C2) of the phenolic OH group. As a consequence, corresponding products **4ar** and

4as were obtained in a regioselective manner in high yields (84–86 %). Similarly, 1,3,5-trimethoxybenzene (**3t**) also reacted smoothly with enamines **2a** and **2e**, which resulted in high yields (81–83 %, Table 3) of corresponding products **4au** and **4eu**.

Next, we turned our efforts towards the development of a convenient method for the preparation of hydropyrido[1,2-*a*]-indole frameworks from simple raw materials. This angular tricyclic building block is a common precursor of a variety of biologically active natural alkaloids and pharmacophores.[12] Therefore, research directed towards the efficient synthesis of this core moiety is a longstanding goal for synthetic organic and medicinal chemists.[8,12,13] In our synthetic exercise, 3-methylindole was employed as a binucleophile in a tandem π-bond isomerization/FC/cyclization reaction with *N*-Bz-protected enamines **2e**–**h**, derived in situ from γ-aminocrotonophenones **1e–h** under our conditions, catalyzed by $B(C_6F_5)_3$. All the reactions furnished satisfactory yields (60–68 %) of corresponding 8,9-dihydropyrido[1,2-*a*]indole building blocks **4eq**–**hq** (Scheme 4).



Scheme 4. One-pot, two-step method for the construction of hydropyrido[1,2-*a*]indole scaffolds possessing an amino group at C9.

Conclusions

We developed a one-pot, two-step sequential approach to access biologically attractive, functionalized γ-heteroaryl/aryl-substituted γ-amino ester/γ-aminoketone derivatives in good to high overall yields. The two-step method proceeds by π-bond isomerization of *N*-benzoyl-protected γ-aminocrotonates/γ-aminocrotonophenones by using Et_3N, followed by tandem π-bond isomerization/Friedel–Crafts reaction of the resultant enamines with a variety of heteroarenes/arenes in the presence of $B(C_6F_5)_3$ as a powerful Lewis acid catalyst. Interestingly, this unprecedented method also constituted easy entry to the pharmacologically important class of 8,9-dihydropyrido[1,2-*a*]indoles in a practical manner. Furthermore, this two-step synthetic process has several advantageous points: it is simple, mild (room temperature), tolerant to functional groups, has a wide substrate scope, provides good to high overall yields, and requires a low catalyst loading (5 mol-%). Enantioselective synthesis as well as application of γ-heteroaryl/aryl-substituted GABA derivatives in medical science is in a preliminary stage, which will be published in due course.

Experimental Section

General Methods: All reactions were performed under an inert atmosphere and were monitored by TLC by using Merck 60 F_{254} precoated silica gel plates (0.25 mm thickness); the products were visualized by UV detection. Flash chromatography was performed with silica gel (200–300 mesh). ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance (III) 400 MHz spectrometer. High-resolution mass spectrometry (HRMS) was performed by using a ESI-TOF mass spectrometer. All catalysts were procured from commercial sources.

Representative Procedure for the Synthesis of Ethyl 4-Benzamido-4-(1*H*-indol-3-yl)butanoate (4aa): A mixture of compound **1a** (0.0466 g, 0.2 mmol) and Et_3N (0.4 mmol, 56.0 μL) in dry toluene (0.2 mL) under an argon atmosphere was heated at 50 °C for 12 h (monitored by TLC). Upon complete consumption of **1a**, triethylamine was evaporated under reduced pressure to give protected enamine **2a**, to which a mixture of indole (**3a**, 0.24 mmol) and $B(C_6F_5)_3$ (0.01 mmol, 5.0 mol-%) in dry CH_2Cl_2 (0.2 mL) was added at room temperature. After 18 h, the mixture was directly purified by column chromatography (silica gel, EtOAc/hexane 1:9) to afford chemically pure **4aa** (0.056 g, 80 %). IR (KBr): $\tilde{\nu}$ = 3317, 2981, 2955, 1719, 1630, 1602, 1578, 1519, 1488, 1459, 1413, 1382, 1323 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.23 (br. s, 1 H), 7.75 (d, J = 7.52 Hz, 2 H), 7.72 (d, J = 8.04 Hz, 1 H), 7.45–7.48 (m, 1 H), 7.37–7.41 (m, 3 H), 7.19–7.23 (m, 2 H), 7.10–7.14 (m, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 5.58–5.62 (m, 1 H), 4.02–4.13 (m, 2 H), 2.37–2.51 (m, 4 H), 1.19 (t, J = 7.28 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.0, 166.8, 136.6, 134.4, 131.5, 128.5, 126.9, 125.9, 122.5, 121.8, 120.0, 119.3, 116.4, 111.4, 60.6, 46.7, 31.5, 29.7, 14.1 ppm. HRMS (ESI): calcd. for $C_{21}H_{22}N_2O_3[M + Na]^+$ 373.1523; found 373.1514.

Supporting Information (see footnote on the first page of this article): All copies of the ^1H NMR and ^{13}C NMR spectra.

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