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DBU-catalyzed Michael addition of bulky glycine imine to α,β-unsaturated isoxazoles and pyrazolamides

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Abstract

A DBU-catalyzed Michael additions of several pronucleophiles with high pK_a values including bulky glycine imines, α-tetra-lone, 1-methyl-2-indolone and nitroalkanes to α,β-unsaturated isoxazoles and pyrazolamides have been realized in THF with 1.0 eq. LiBr as a additive at room temperature within 3 h to provide Michael adducts in excellent yields (up to 97%) and diastereoselectivities (> 20:1).

Keywords

Michael addition; glycine imine; α,β-unsaturated isoxazole; α,β-unsaturated pyrazolamide; DBU

Introduction

IBase-catalyzed Michael addition has played a key role in modern organic synthesis due to its powerful C-C and C-X (X = N, O, S, P etc.) bond formations [1-5]. Metal or metal-free catalyzed Michael additions have been well documented by many chemists [6-10]. The activated methylene compounds such as 1,3-dicarbonyl compounds, α-nitro- and α-cyanoesters are the most common Michael donors and used as pronucleophiles to attack electron-deficient alkenes in the presence of suitable catalysts [11-16]. These substrates with an acidic H and low pK_a values are easily deprotonated to be carbon anions to take apart in Michael reactions. However, substrates with high pK_a values, for examples, glycine imines, aromatic ketones, nitroalkanes are challenging Michael donors for base-catalyzed Michael additions because of their low acidity [17-19]. 1,8-bis(dimethylamino)naphthalene (DMAN), 1,4-diazabicyclo [2.2.2]octane (DABCO) 1,8-diazabicyclo[5.4.0] undec-7-ene (DBU) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) are usually regarded as superbases for deprotonation of these above-mentioned pronucleophiles with high pK_a values in base-catalyzed Michael reactions [20-25]. On one hand, the benzophenone-protected glycine derivatives (glycine imines) as readily available starting materials were used in many tranformations including alkylation [26, 27], [3+2] cycloaddition [28-30] and Michael addition [31-39]. In these Michael reactions, acrylates and acrylamides, unsaturated nitriles and esters, linear and cyclic enones, vinyl phenyl sulfone, and aromatic nitroalkenes have been applied as Michael acceptors. On the

other hand, compounds with isoxazole and pyrazole ring exhibit a wide range of biological activities [40-43], such as anticancer, antimicrobial and anti-inflammatory effects (Figure 1). By using glycine imines **1** and α,β-unsaturated isoxazoles **2** or pyrazolamides **3** as starting materials, many unnatural amino acids can be generated and severed as

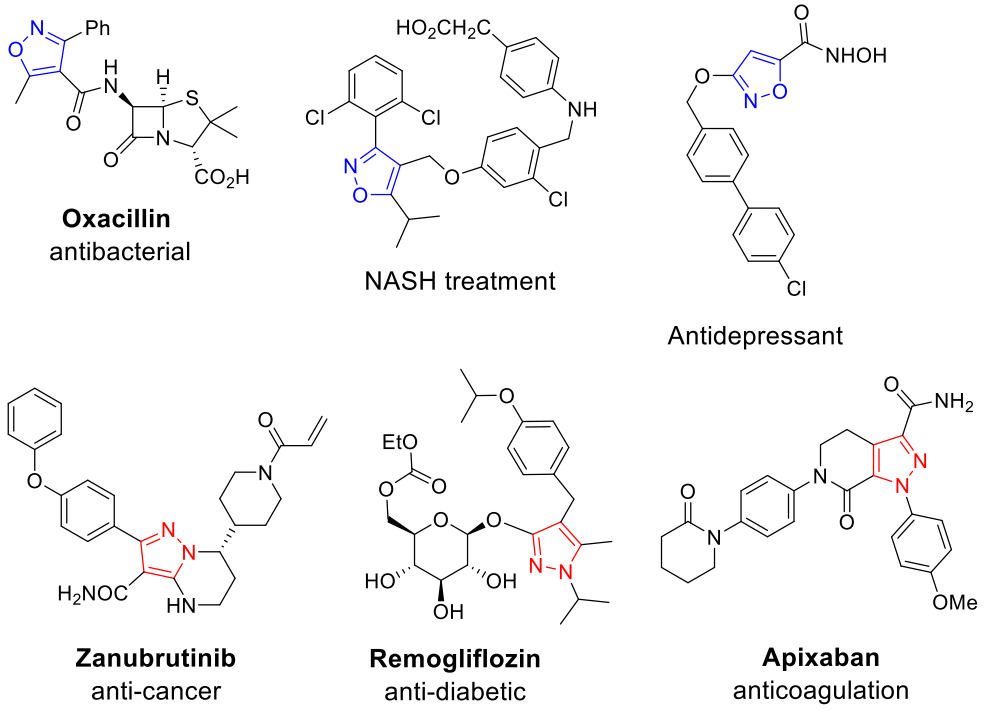


Figure 1: Representative drugs and compounds containing isoxazole and pyrazole core.

building blocks for some new chemical moieties with unique bio-activities. Adamo and colleagues [44, 45] have used styrylisoxazoles **2** as cinnamate equivalents with high reactivity towards soft nucleophiles such as enolates, nitroalkanes, isocyanoacetate, and indoles in Michael reactions. Du's group [46] have developed DBU-catalyzed glycine imines to aromatic nitroalkenes with LiOTf as an additive to afford Michael adducts in high yields and moderate diastereoselective ratios in 24 h. Li and coworkers [47] have reported a highly enantioselective Michael addition of α-nitroacetate to activated α,β-unsaturated pyrazolamide catalyzed by a bifunctional

squaramide to produce Michael adducts with excellent yields but without diastereoselectivties (dr = 1:1 for all cases), and the reaction is very sluggish (up to 168 h). Recently, we have developed tandem grinding reactions involving aldol condensation and Michael addition in sequence for preparation of 3,4,5-trisubstituted isoxazoles [48]. For our continue effort to introduce heterocyclic rings to linear organic molecules, herein, we have reported DBU-catalyzed highly diastereoselective *syn*-Michael reactions between α,β-unsaturated isoxazoles **2** or pyrazolamides **3** with several types of substrates with high pK_a values including glycine imines, α-tetralone, 1-methyl-2-indolone and nitroalkanes under very mild conditions by using LiBr as a additive in THF (Figure 2).

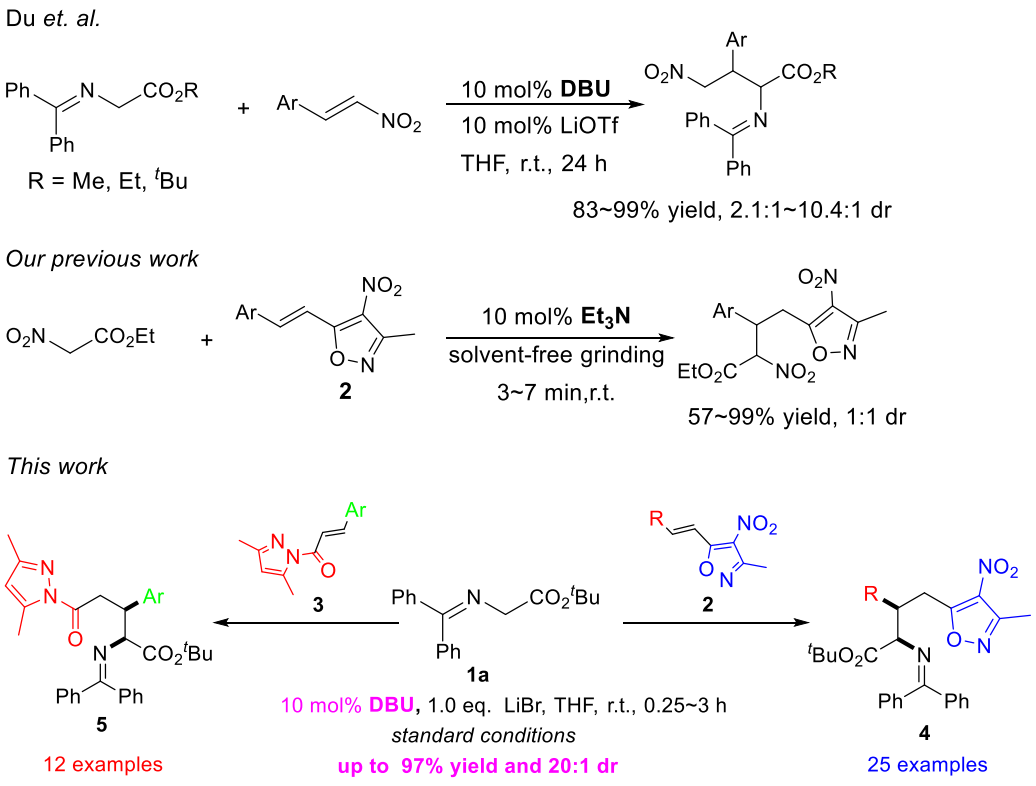


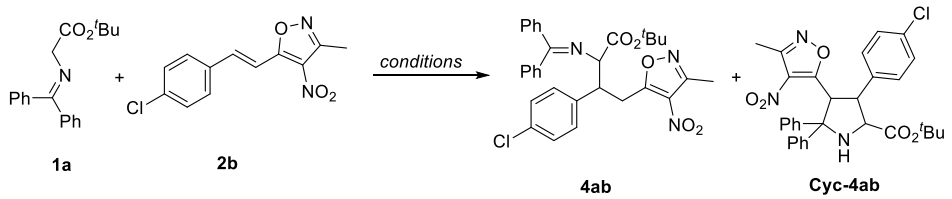
Figure 2: Base catalyzed Michael addition of glycine imine **1a**.

Results and Discussion

Initially, glycine imine **1a** and styrylisoxazole **2b** were used as substrates for the reaction conditions optimization of Michael addition, and the results are shown in Table 1. When the reactions of **1a** and **2b** were performed in CH_2Cl_2 at room temperature in the presence of Et_3N or $^iPr_2NEt$, no Michael adduct **4ab** was found within 24 h (Table 1, entries 1-5). The product **4ab** was obtained by using 1.0 eq. Cs_2CO_3 as base but with very low yield (11%, entry 6). No product was obtained when DABCO as a stronger base than Et_3N was used in the reaction (entries 7 and 8). The combination of catalytic amount of DABCO (10 mol%) and Cs_2CO_3 (10 mol%) has still given a disappointed result even with a long reaction time (entry 9). To our delight, **4ab** was obtained in 62% yield when the increase of Cs_2CO_3 from 0.1 eq. to 1.0 eq., but with 16% yield of a accompanied [3+2] cyclo-addition product **Cyc-4ab** (entry 10). Both the yields of Michael adduct **4ab** and cyclization adduct **Cyc-4ab** were increased with the increased use of DABCO from 0.1 eq. to 1.0 eq. (entry 11, 75% and 18%). By replacing DABCO and Cs_2CO_3 with 10 mol% of DBU, **4ab** and **Cyc-4ab** were obtained in 71% and 14% yields, respectively (entry 12). The yields of **4ab** and **Cyc-4ab** were promoted with the increase use of DBU in a short reaction time (entry 13 *vs* entry 12). In order to improve the yield of cyclization adduct **Cyc-4ab**, 2.5 eq. of DBU was used, but no significant change of the yields of **4ab** and **Cyc-4ab** was found (entry 14 *vs* entries 12 and13). Du and co-workers have reported a DBU-catalyzed Michael reaction of glycine imine **1a** and *trans*-β-nitrostyrene in the presence of LiOTf to provide Michael adducts in high yields and good diastereoselective ratios (up to 99% yield and 10.4:1 dr) [31, 46]. Inspired by their research, 10 mol% LiBr was used as a addictive to afford **4ab** in 69% yield with trace of cyclization product **Cyc-4ab** (entry 15). It was found that the addition of LiBr can

suppress [3+2] cyclo-addition of two substrates **1a** and **2b**. This pheromone is very different to metal-catalyzed [3+2] cyclo-addition of nitroolefins with glycine imines [49, 50]. When the amount of LiBr was increased from 0.1 eq. to 1.0 eq., the yield of **4ab** was up to 81% in CH_2Cl_2 (entry 16). Switching CH_2Cl_2 to THF, the Michael adduct **4ab** was formed almost in quantitative yield (95%) within half an hour (entry 17) under room temperature. The yield of **4ab** was decreased by using 1.0 eq. LiCl as a additive (entry 18). LiOTf can furnish **4ab** in a comparable yield with LiBr as a additive (entry 19), however, LiBr is cheaper and more moisture-stable than LiOTf. Due to a very bulky hinderance of *tert*-butyl group in **1a**, the above-obtained distereo-ratios of **4ab** are beyond 20:1. Therefore, the optimal reaction conditions for the Michael addition of **1a** and **2b** were established as follows: 10 mol% DBU, 1.0 eq. LiBr, THF, room temperature and proper reaction time.

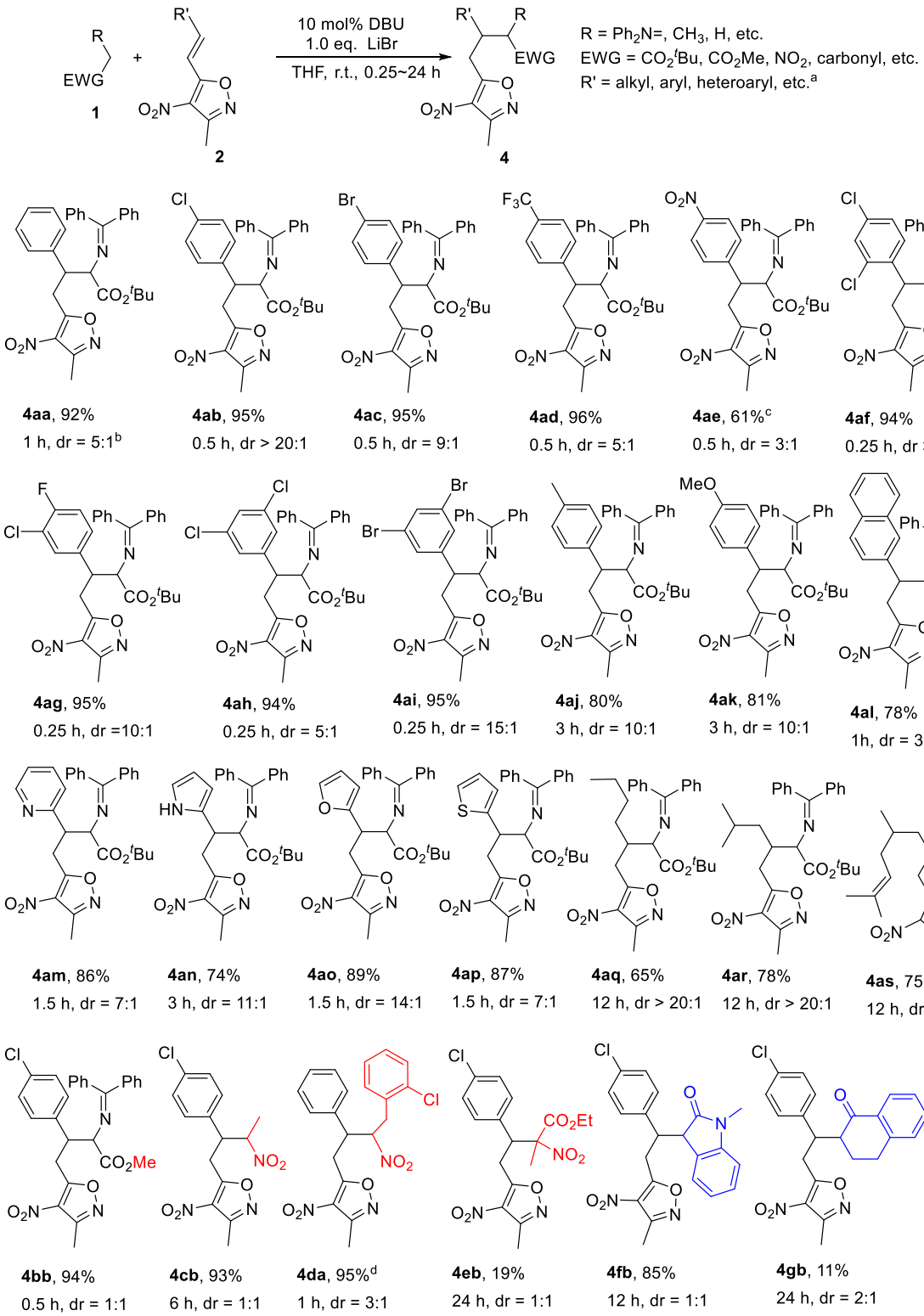
Table 1: The screening of reaction conditions.



entry[a]	Base	additive	solvent	*T*/time	**4ab** (%)[b,c]	**Cyc-4ab** (%)[b]
1	Et_3N (0.1 eq.)	-	CH_2Cl_2	25 °C/24 h	0	0
2	Et_3N (0.3 eq.)	-	CH_2Cl_2	25 °C/24 h	0	0
3	Et_3N (1.0 eq.)	-	CH_2Cl_2	25 °C/24 h	0	0
4	$^iPr_2NEt$ (1.0 eq.)	-	CH_2Cl_2	25 °C/24 h	0	0
5	$^iPr_2NEt$ (2.0 eq.)	-	CH_2Cl_2	25 °C/24 h	0	0
6	-	Cs_2CO_3 (1.0 eq.)	CH_2Cl_2	25 °C/24 h	11	0
7	DABCO (0.1 eq.)	-	CH_2Cl_2	25 °C/24 h	0	0
8	DABCO (1.0 eq.)	-	CH_2Cl_2	25 °C/24 h	0	0
9	DABCO (0.1 eq.)	Cs_2CO_3 (0.1 eq.)	CH_2Cl_2	25 °C/48 h	0	0
10	DABCO (0.1 eq.)	Cs_2CO_3 (1.0 eq.)	CH_2Cl_2	25 °C/48 h	62	16
11	DABCO (1.0 eq.)	Cs_2CO_3 (1.0 eq.)	CH_2Cl_2	25 °C/24 h	75	18
12	DBU (0.1 eq.)	-	CH_2Cl_2	25 °C/24 h	71	14
13	DBU (1.0 eq.)	-	CH_2Cl_2	25 °C/12 h	76	15
14	DBU (2.5 eq.)	-	CH_2Cl_2	25 °C/12 h	77	17
15	DBU (0.1 eq.)	LiBr (0.1 eq.)	CH_2Cl_2	25 °C/12 h	69	trace
16	DBU (0.1 eq.)	LiBr (1.0 eq.)	CH_2Cl_2	25 °C/6 h	81	trace
17	**DBU (0.1 eq.)**	**LiBr (1.0 eq.)**	**THF**	**25 °C/0.5 h**	**95**	**trace**
18	DBU (0.1 eq.)	LiCl (1.0 eq.)	THF	25 °C/2 h	88	trace
19	DBU (0.1 eq.)	LiOTf (1.0 eq.)	THF	25 °C/2 h	93	trace

a. The reaction was conducted in 0.1 mmol scale at r.t. for proper reaction time. Unless otherwise noted, the amount of **2b** was equimolar with that of glycine imine **1a**. b. Isolated yield based on **1a**. c. The diastereo-ratio of **4ab** is up to 20:1 which was determined by ^{1}HNMR.

With the optimal conditions in hand, various α,β-unsaturated isoxazoles **2a-s** as substrates were used in the Michael addition of **1a** to provide **4a-s** in moderate to excellent yields (45~95%) and distereo-ratios (> 20:1), and the results were listed in Figure 3. From Figure 3, it was found that α,β-unsaturated isoxazoles with an aromatic ring at β-position to give Michael products in higher yields than substrates



a. The reaction was conducted in 0.1 mmol scale at r.t. for proper reaction time. Unless otherwise noted, the amount of **2** was equimolar with that of glycine imine **1**. b. Isolated yield based on **1**, and the diastereo-ratios were determined by ^{1}HNMR. c. The low yield of **4ae** (61%) is due to the cyclization reaction during the flash column chromatographic purification process. d. 1.0 eq. DBU was used without addition of LiBr.

Figure 3: DBU-catalyzed Michael additions of **1** and **2**.

with one alkyl substituent at β-position (for example, **4ab** vs **4aq**, 95% vs 65%) within 3 h. Substrates containing one hetero-aromatic ring such as pyridine (**2m**), pyrrole (**2n**), furan (**2o**) and thiophene (**2p**) are also suitable to this reaction to afford products in good to high yields (74-89%). Substrates **2q**-**s** are less active than **2b** and the other α,β-unsaturated isoxazoles in this Michael reaction, and they need relative long reaction time to give the corresponding products (up to 24 h). When the R group in glycine imine **1a** was changed from *tert*-butyl to methyl (**1b**), the diastereo-ratio of product is dramatically decreased from 20:1 to 1:1 but with excellent yield (**4bb**, 94%). Some challenging substrates including nitroalkanes **1c** and **1d**, α-nitro ethyl acetate **1e**, N-methylindolin-2-one **1f** and 1-tetralone **1g** were also used in this DBU-catalyzed Michael addition to provide the corresponding products in high yields except **4eb** (19%) and **4gb** (11%).

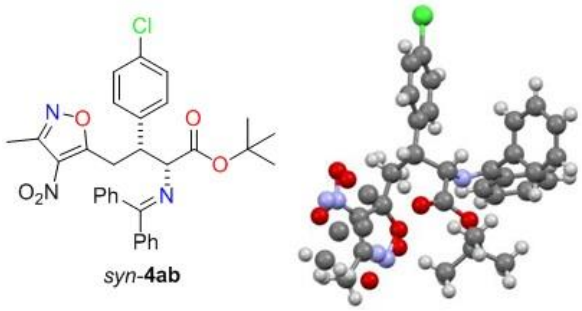
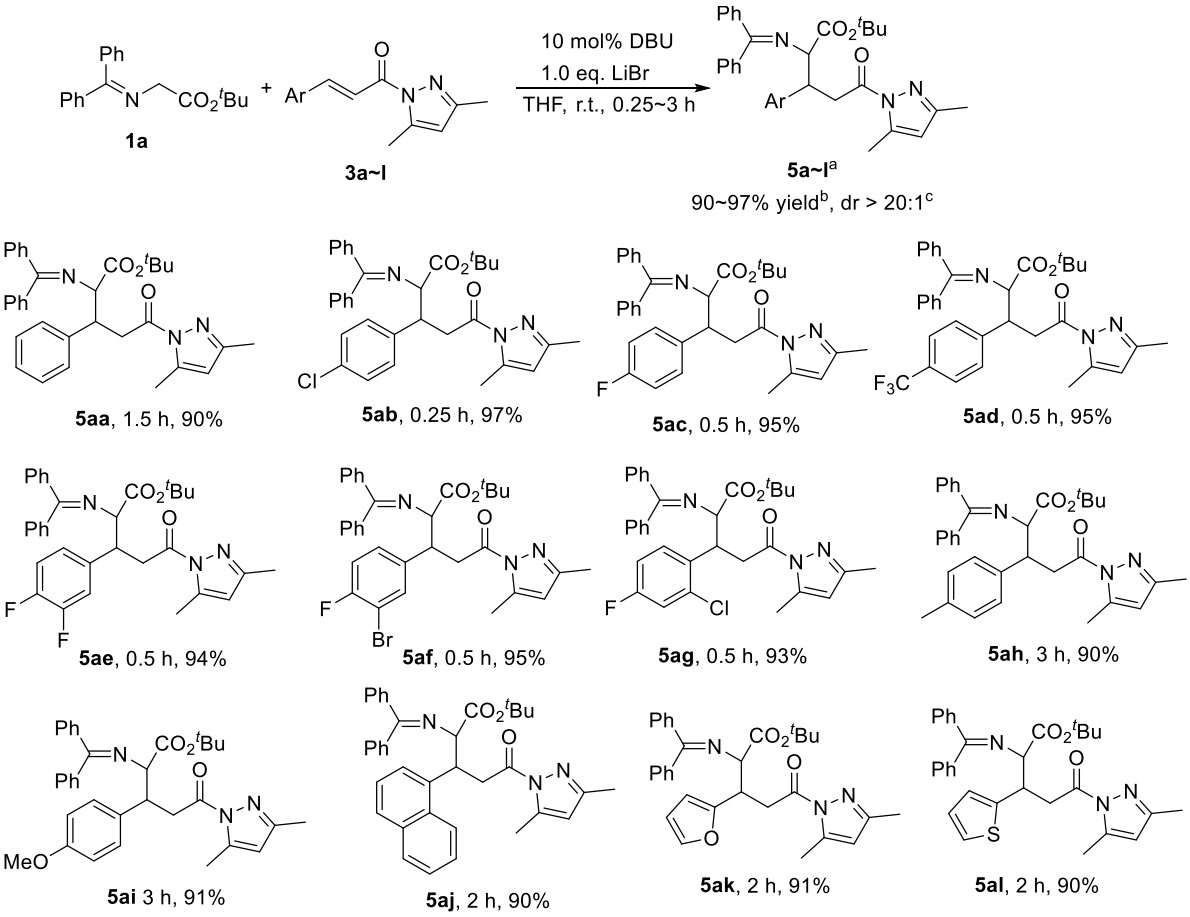


Figure 4: The X-ray structure of *syn*-**4ab**.

In order to know the relative configuration of Michael adducts, the single crystal of **4ab** was cultivated from the mixed solvent of petroleum ether and CH_2Cl_2 which is suitable for X-ray diffraction analysis [51]. Owing to the poor quality of single crystal, some disorder was found during the analysis process, however, the X-ray single crystal diffraction diagram obviously indicated that the *syn*-addition is predominated in this LiBr-assisted DBU-catalyzed Michael reaction (Figure 4). This phenomena is contrary to previous reports by Du's group and Kyungsoo with colleagues [45, 49], in their researches, the reactions of *trans*-nitrostyrenes with glycine imine **1a** exclusively

provide *anti*-adducts. The reason to *syn*-addition may due to the dynamic control in the reaction process with a relative short reaction time (0.25~3 h for most cases).



a. The reaction was conducted in 0.1 mmol scale at r.t. for proper reaction time. Unless otherwise noted, the amount of **3** was equimolar with that of glycine imine **1a.** b. Isolated yield based on **1a.** c. The diastereo-ratios were determined by 1HNMR.

Figure 5: DBU-catalyzed Michael additions of **1a** and **3**.

Pyrazole and derivatives have presented many types of bioactivities, and α,β-unsaturated pyrazolamides **3** have been used as substrates for construction of molecules with pyrazole core. Encouraged by the above success of Michael additions between bulky glycine imine **1a** and α,β-unsaturated isoxazoles **2**, α,β-unsaturated pyrazolamides **3** were used as Michael acceptors under the optimal reaction conditions, **5a-k** (Figure 5) were obtained in excellent yields (93~97%) and diastereo-ratios (> 20:1), and no cyclization product was found in all cases. Substrates (**3b-g**) with electron-withdrawing groups on their aromatic ring have furnished corresponding products (**5b-g**) in excellent yields within 0.5 h, but substrate **3h** with an electron-

donating group (4-OMe) is less active than **3b-g** to give Michael adduct **5h** in three hours. Substrates with one furan (**3j**) or thiophene (**3k**) are tolerated in this reaction to provide **5j** and **5k** in good yields within two hours.

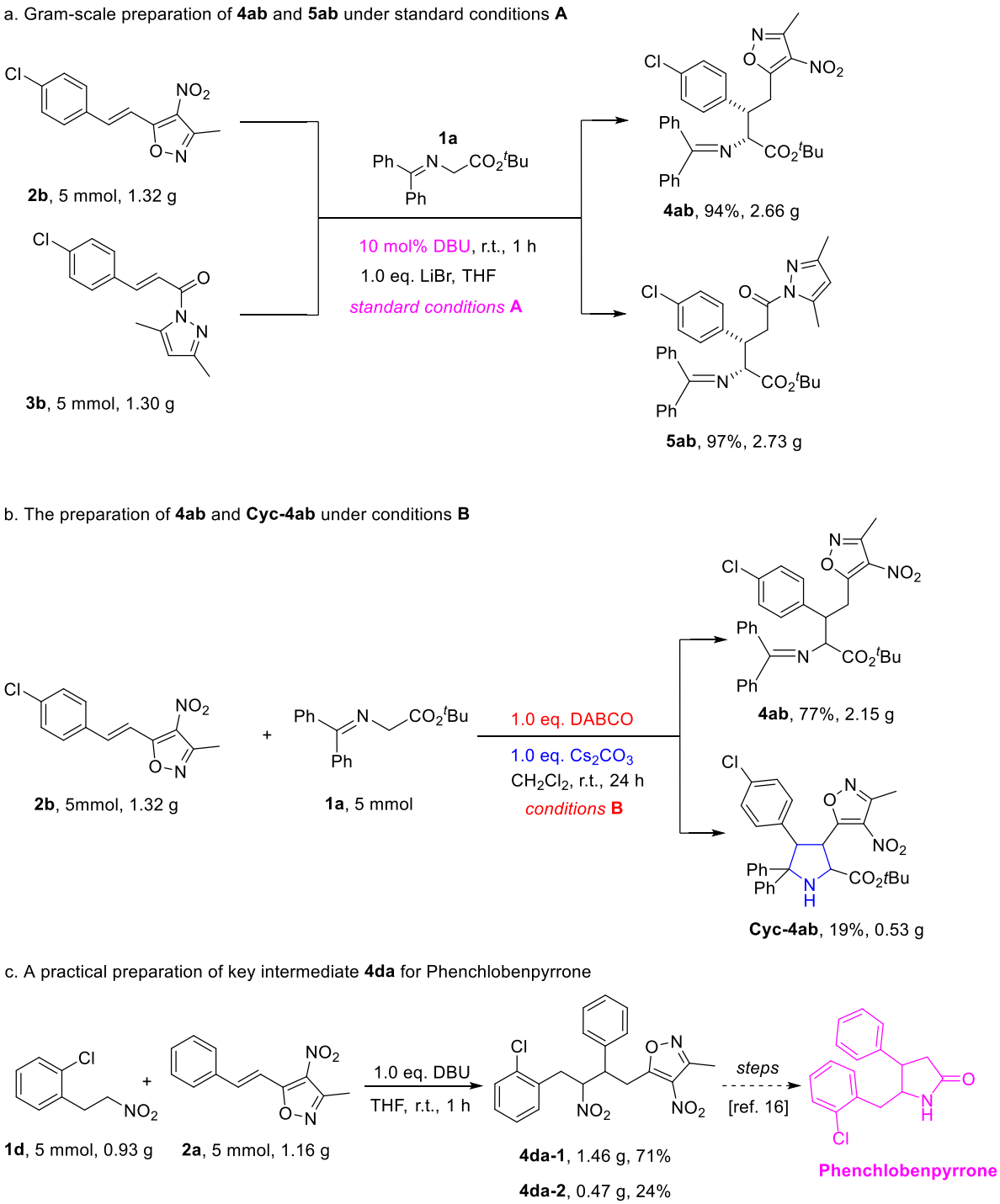


Figure 6: The practical synthetic use of Michael additions of **1**.

In order to show the practical synthetic value of this Michael reaction, gram-scale preparation of **4ab** and **5ab** were conducted (Figure 6a), **4ab** and **5ab** were obtained in excellent yields (94% and 97% yield) within one hour under standard conditions (A). When the reaction was performed under conditions B (1.0 eq. DABCO, 1.0 eq. Cs_2CO_3, CH_2Cl_2, r.t., 24 h), Michael adduct **4ab** and cyclization product **Cyc-4ab** were obtained as 4:1 ratio (Figure 6b). Phenchlobenpyrrone and derivatives [52] have been regarded as one new type of potential treatment for depression and Alzheimer syndrome. The key intermediate **4da** for Phenchlobenpyrrone was prepared from nitroalkane **1d** and styrylisoxazole **2a** in 95% overall yield in the presence of 1.0 eq. of DBU in THF under r.t. in 1 hours. Two diastereomers of **4da** (**4da-1** and **4da-2**) were obtained as 3:1 ratio through a flash column chromatographic purification process (Figure 6c).

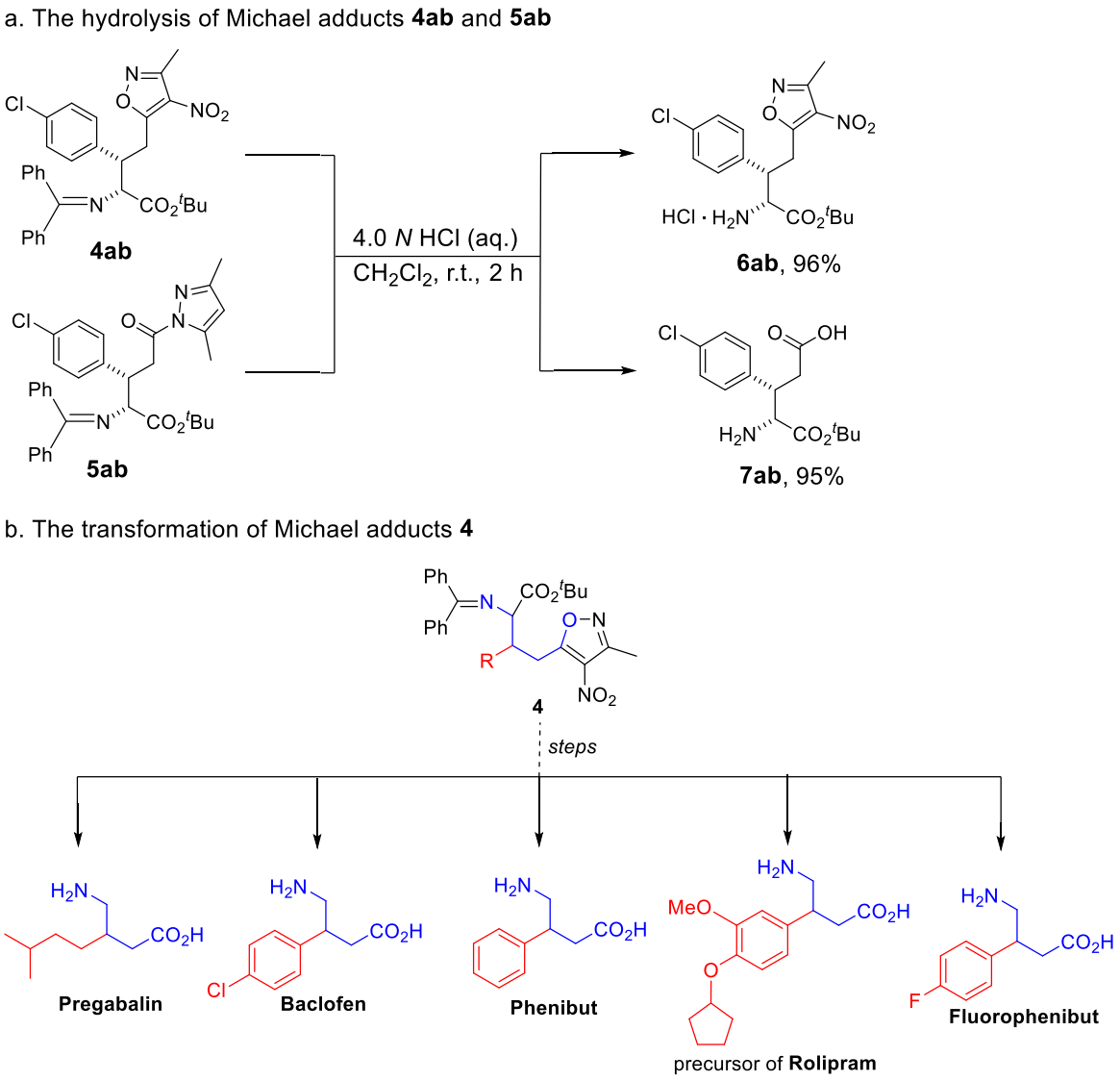


Figure 7: The transformations of Michael adducts **4** and **5**

In the presence of 4.0 N of HCl in CH_2Cl_2, the Michael adducts **4ab** and **5ab** can be converted to be their hydrochlorides **6ab** and **7ab** in almost quantitative yield, respectively (Figure 7a). Interestingly, imine and pyrozole ring in **5ab** were hydrolyzed at the same time under acidic conditions. Pregabalin, Baclofen, Phenibut, Fluorophenibut and Rolipram contain the same common core of γ-aminobutanoic acid (GABA), these compounds have been widely used in clinic treatment for neuro-diseases [53-56]. Isoxazole and pyrazole in the Michael adducts **4** and **5** have been used as the mask of carboxylic group, so the Michael adducts **4** and **5** could serve as

the precursors and transform to be these analogues of γ-aminobutanoic acid through hydrolysis and decarboxylation process (Figure 7b).

Conclusion

In conclusion, we have developed an efficient DBU-catalyzed *syn*-Michael addition of α,β-unsaturated isoxazoles or pyrazolamides with a bulky glycine imine to provide Michael adducts in good to excellent yields and diastereoselectivities in THF by using LiBr as a additive. Several types of substrates with high pK_a values like nitroalkanes and N-methylindolin-2-one were also used as Michael donor in the above-mentioned addition. A practical preparation of a key intermediate for Phenchlobenpyrrone has been realized based on this DBU-assisted Michael reaction. These Michael adducts can be converted into various bioactive molecules through several simple steps. The asymmetric version of these Michael additions have been presently investigated in our laboratory.

Experimental

To a solution of glycine imine **1a** (0.5 mmol) and α,β-unsaturated isoxazoles **2b** (0.5 mmol) in 5.0 mL of THF, 7.5 uL of DBU (10 mol%, 0.1 eq.) and LiBr (44 mg, 1.0 eq., 0.5 mmol) were added successively. The mixture is stirred at room temperature for 0.5 h, and the reaction was monitored by TLC. When TLC indicates that starting materials were consumed, the solvent was evaporated under reduced pressure and the residue was purified through a flash column chromatography (petroether/ethyl acetate = 10:1 to 5: 1, v/v). The pure product **4ab** was obtained as a white foam.

Supporting Information

Supporting information text

Supporting Information File 1: Characterization data and copies of 1H, 13C, 19F NMR spectra and HRMS for all new compounds, X-ray crystal structure data of **4ab**.

File Format: Word

Supporting Information File 2: Checkcif files of **4ab**

File Format: PDF

Acknowledgements

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