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Authors  Yu-Jun Bai, Mei-Ling Cheng, Xiao-Mu Hu, Ya-Jun Bai, Xiao-Hui
Zheng, Sheng-Yong Zhang and Ping-An Wang

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ORCID® iDs  Ping-An Wang - https://orcid.org/0000-0003-3255-1889
DBU-catalyzed Michael addition of bulky glycine imine to α,β-unsaturated isoxazoles and pyrazolamides

Yu-Jun Bai¹,², Mei-Ling Cheng², Xiao-Mu Hu²,³, Ya-Jun Bai¹, Xiao-Hui Zheng¹, Sheng-Yong Zhang*² and Ping-an Wang*²

Address: ¹Key Laboratory of Resource Biology and Biotechnology in Western China, Ministry of Education, The College of Life Sciences, Northwest University, Xi'an 710069, P. R. China. ²Department of Medicinal Chemistry, School of Pharmacy, Fourth Military Medical University, Xi'an 710032, P. R. China. ³Department of Pharmacy, Fuzong Clinical Medical College of Fujian Medical University (900 Hospital of the Joint Logistics Team), Fuzhou 350025, P. R. China.

Email: Ping-An Wang – ping_an1718@outlook.com

* Corresponding author

Abstract

A DBU-catalyzed Michael additions of several pronucleophiles with high pKa 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 transformations 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

![Oxacillin antibacterial](image)

![NASH treatment](image)

![Antidepressant](image)

![Zanubrutinib anti-cancer](image)

![Remogliflozin anti-diabetic](image)

![Apixaban anticoagulation](image)

**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, isocyanooacetate, 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 diastereoselectivities (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 pKₐ values including glycine imines, α-tetralone, 1-methyl-2-indolone and nitroalkanes under very mild conditions by using LiBr as an additive in THF (Figure 2).

Du et al.

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{CO}_2\text{R} \\
\text{R} = \text{Me, Et, } & \quad \text{Bu} \\
\text{Ph} & \quad \text{Ar} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{O}_2\text{N} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

83–99% yield, 2.1:1–10.4:1 dr

Our previous work

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{CO}_2\text{Et} \\
\text{O}_2\text{N} & \quad \text{CO}_2\text{R} \\
\text{Ar} & \quad \text{Ar} \\
\text{NO}_2 & \quad \text{NO}_2 \\
\text{O}_2\text{N} & \quad \text{NO}_2 \\
\text{Ar} & \quad \text{Ar}
\end{align*}
\]

57–99% yield, 1:1 dr

This work

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{Ar} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{Ar} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{Ar} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{Ar}
\end{align*}
\]

12 examples

10 mol% DBU, 1.0 eq. LiBr, THF, r.t., 0.25–3 h
standard conditions
up to 97% yield and 20:1 dr

25 examples

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 CH₂Cl₂ at room temperature in the presence of Et₃N or tPr₂NEt, no Michael adduct 4ab was found within 24 h (Table 1, entries 1-5). The product 4ab was obtained by using 1.0 eq. Cs₂CO₃ as base but with very low yield (11%, entry 6). No product was obtained when DABCO as a stronger base than Et₃N was used in the reaction (entries 7 and 8). The combination of catalytic amount of DABCO (10 mol%) and Cs₂CO₃ (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 Cs₂CO₃ 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 Cs₂CO₃ 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 and 13). 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 additive 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 CH2Cl2 (entry 16). Switching CH2Cl2 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 | Base          | additive       | solvent | T/time | 4ab (%)b,c | Cyc-4ab (%)b |
|-------|---------------|----------------|---------|--------|------------|--------------|
| 1     | Et3N (0.1 eq.) | -              | CH2Cl2  | 25 °C/24 h | 0          | 0            |
| 2     | Et3N (0.3 eq.) | -              | CH2Cl2  | 25 °C/24 h | 0          | 0            |
| 3     | Et3N (1.0 eq.) | -              | CH2Cl2  | 25 °C/24 h | 0          | 0            |
| 4     | ’Pr2NEt (1.0 eq.) | -         | CH2Cl2  | 25 °C/24 h | 0          | 0            |
| 5     | ’Pr2NEt (2.0 eq.) | -         | CH2Cl2  | 25 °C/24 h | 0          | 0            |
| 6     | -              | Cs2CO3 (1.0 eq.) | CH2Cl2  | 25 °C/24 h | 11         | 0            |
| 7     | DABCO (0.1 eq.) | -              | CH2Cl2  | 25 °C/24 h | 0          | 0            |
| 8     | DABCO (1.0 eq.) | -              | CH2Cl2  | 25 °C/24 h | 0          | 0            |
| 9     | DABCO (0.1 eq.) | Cs2CO3 (0.1 eq.) | CH2Cl2  | 25 °C/48 h | 0          | 0            |
| 10    | DABCO (0.1 eq.) | Cs2CO3 (1.0 eq.) | CH2Cl2  | 25 °C/48 h | 62         | 16           |
| 11    | DABCO (1.0 eq.) | Cs2CO3 (1.0 eq.) | CH2Cl2  | 25 °C/24 h | 75         | 18           |
| 12    | DBU (0.1 eq.) | -              | CH2Cl2  | 25 °C/24 h | 71         | 14           |
| 13    | DBU (1.0 eq.) | -              | CH2Cl2  | 25 °C/12 h | 76         | 15           |
| 14    | DBU (2.5 eq.) | -              | CH2Cl2  | 25 °C/12 h | 77         | 17           |
| 15    | DBU (0.1 eq.) | LiBr (0.1 eq.)  | CH2Cl2  | 25 °C/12 h | 69         | trace        |
| 16    | DBU (0.1 eq.) | LiBr (1.0 eq.)  | CH2Cl2  | 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 1H NMR.

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

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 diastereoisomer ratios were determined by $^1$H NMR. 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.
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 diastereomeric 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 CH₂Cl₂ 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).

![Chemical structures and reaction equilibrium](image)

**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.

a. Gram-scale preparation of 4ab and 5ab under standard conditions A

\[
\begin{align*}
2b, \ 5 \ \text{mmol}, \ 1.32 \ \text{g} \\
3b, \ 5 \ \text{mmol}, \ 1.30 \ \text{g}
\end{align*}
\]

b. The preparation of 4ab and Cyc-4ab under conditions B

\[
\begin{align*}
2b, \ 5 \ \text{mmol}, \ 1.32 \ \text{g} \\
1a, \ 5 \ \text{mmol}
\end{align*}
\]

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$_2$CO$_3$, CH$_2$Cl$_2$, 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).
a. The hydrolysis of Michael adducts 4ab and 5ab

![Chemical structures and reactions]

b. The transformation of Michael adducts 4

![Chemical structures and reactions]

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

In the presence of 4.0 N of HCl in CH$_2$Cl$_2$, 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 pyrazole 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 neurodiseases [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 pKa 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 Phenchlobenpyrrrone 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

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