Communication

DBU Promoted Polysubstituted Arene Formation via a Michael Addition/Cyclization/Elimination Cascade Reaction

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Abstract: The straightforward construction of polysubstituted arenes is essential in both synthetic chemistry and medicinal chemistry. Herein, we reported a DBU promoted Michael addition/cyclization/elimination cascade reaction between vinylogous malononitrile derivatives and chlorinated nitrostyrenes for the synthesis of polysubstituted arenes. The method features mild reaction conditions, wide substrate scope and high yield. Interestingly, preliminary study of the enantioselective version of this cascade was conducted to give chiral biaryl atropisomers with up to 40% ee through center-to-axial chirality transfer strategy.

Keywords: Michael addition; arenes; nitrostyrene; axial chirality

1. Introduction

The construction of arenes with different complexity is the main focus in both synthetic chemistry and medicinal chemistry [1–4], as the high frequency of the appearance of arenes in numerous valuable molecules [5–8]. Although lots of methodologies have been developed in this area, the facile synthesis of polysubstituted arenes usually relies on the inconvenient stepwise substitution of existed arenes [9–12]. Thus, the straightforward formation of arene cores with readily obtainable pre-functionalized substrates could enhance the synthetic efficiency and facilitate the development in this area.

Recently, the easily accessible α-brominated and chlorinated nitrostyrenes 1 and 2 [13,14] were emerged as powerful C2 synthons in the synthesis of different ring systems (Figure 1a). In particular, with the utilization of different C3 synthons, a series of polysubstituted heteroarenes were constructed through (3 + 2) cyclization process, including furans [15–18], pyrazoles [19–21], imidazoles [22], triazoles [23–25], and pyrroles [26–30]. The versatilities of nitrostyrenes 1-2 were based on the electron deficiency of the double bound and the high reactivity of the leaving group X (X= Cl, Br) [31–33]. Unfortunately, the construction of important polysubstituted arenes with these easily accessible nitrostyrenes were still undeveloped, probably due to the lack of suitable C4 synthons.

With the ongoing interest of our group in the chemistry of chlorinated nitrostyrene 1 [34,35], we hypothesized that the vinylogous malononitrile derivative 3 could undergo Michael addition with nitrostyrene 1 to form the adduct 4 in the presence of suitable base, then the base promoted intramolecular cyclization process could give the diastereomers 5 and 6 (Figure 1b). The final 1,2-trans elimination would furnish the polysubstituted arenes 7-8, respectively. In this process, the diastereoselective control in the cyclization step was the key point to avoid the formation of the mixture of arenes 7 and 8. Interestingly, with the chiral catalyst, the enantioselective Michael addition/cyclization/elimination cascade gave
the opportunity to construct chiral biaryl atropisomers through center-to-axial chirality transfer process [36,37] (Figure 1b). Herein, we reported the preliminary results of this interesting cascade reaction.

![Figure 1. Recent development of bromo- or chlorinated nitrostyrenes in (hetero)arene synthesis.](image)

2. Results and Discussion

To test our hypothesis, the initial reaction was conducted with 2-(3,4-dihyronaphthalen-1(2H)-ylidene) malononitrile 3a with simple chlorinated nitrosoyrene 1a in the presence of stoichiometric amount of triethylamine (Et₃N) in dichloromethane at room temperature (Table 1, entry 1). Unfortunately, no desired product 7aa was detected, probably due to the weak basicity of Et₃N. Next, 1,4-Diazabicyc[2.2.2]octane (DABCO) instead of Et₃N was used in the reaction, and the nitro group substituted product 7aa was obtained in 29% yield in 2 h (Table 1, entry 2). With this promising result, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) with enhancing basicity was tested to furnish 7aa in 80% yield within 30 min, and no chlorinated arene derivative 8aa was observed (Table 1, entry 3). However, when stronger base lithium t-butoxide was added into the reaction, only trace amount of 7aa was observed (Table 1, entry 4). In order to further improve the yield, a series of inorganic bases were investigated, but very poor results were obtained (Table 1, entry 5–8). With DBU as the best choice of base, the solvent was then screened (Table 1, entry 9–12), and the utilization of toluene improved the yield of 7aa to 85% within 15 min. In addition, enhancing the equivalent of DBU from 1.0 to 1.5 finally gave the desired product 7aa in 95% yield.

With the optimized conditions in hand, the scope of vinylogous malononitrile derivative 3 and chlorinated nitrostyrenes 1 were explored. The results were summarized in Scheme 1. Both electron-withdrawing and electron-donating substituents in the phenyl ring of nitrostyrenes 1 were compatible in this reaction, and the resulting products were obtained in 70–97% yields (7ba-7ma). In general, the reaction proceeded better with electron-withdrawing groups compared with the electron-donating groups. Meanwhile, the yields of the products decreased in the order of para-substituent, meta-substituent, and ortho-substituent, probably due to the steric hindrance (7ba, 7la, and 7ia). Considering the importance of heterocyclic compounds in medicinal chemistry, the furan [38,39], thiophene [40–43], and indole [44–47] moieties were all installed to the arenes, and the desired products 7na-7qa were furnished in 36–93% yields. On the other hand, the tolerance of vinylogous malononitrile derivative 3 were also investigated. Generally, the substituents on the phenyl ring had few influences in the yields of the products (7ab-7ae). The oxa-malononitrile derivatives were also suitable for this reaction, and the corresponding products 7af and 7ag were obtained in 86% and 68% yields, respectively. Interestingly, compared with the seven-membered ring fused malononitrile derivative, the five-membered ring fused one gave the product with much lower yields (7ah vs. 7ai) with currently unknown reason.
Table 1. Optimization of the reaction conditions.

| Entry | Solvent | Base           | Reaction Time (h) | Yield b (%) |
|-------|---------|----------------|-------------------|-------------|
| 1 c   | DCM     | Et$_3$N        | 12                | trace       |
| 2     | DCM     | DABCO          | 2                 | 29          |
| 3     | DCM     | DBU            | 0.5               | 80          |
| 4     | DCM     | (CH$_3$)$_3$COLi | 12               | trace       |
| 5     | DCM     | NaOH           | 12                | trace       |
| 6     | DCM     | K$_2$CO$_3$    | 12                | trace       |
| 7     | DCM     | CsCO$_3$       | 12                | 16          |
| 8     | DCM     | K$_3$PO$_3$    | 12                | trace       |
| 9 d   | EA      | DBU            | 0.5               | 81          |
| 10    | CH$_3$CN| DBU            | 0.25              | 80          |
| 11 e  | DCE     | DBU            | 0.25              | 82          |
| 12    | Toluene | DBU            | 0.25              | 85          |
| 13 f  | Toluene | DBU            | 0.25              | 95          |

* a Reaction conditions: 1a (0.12 mmol), 3a (0.10 mmol), and base (0.10 mmol) were stirred in solvents (1.0 mL) at room temperature. b Isolated yield. c DCM = dichloromethane. d DCE = 1,2-dichloroethane. e EA = ethyl acetate. f DBU (0.15 mmol) was added.

With these results in hand, the mechanism which was responsible for the dominant formation of the nitro-substituted arene 7 in this Michael addition/cyclization/elimination cascade was proposed (Scheme 2). After the formation of the first Michael adduct, two possible transition states TS-1 and TS-2 could be generated. In TS-2, the DBU spontaneously activated the α-position of nitro group and the electron-deficient nitrile group via the hydrogen bonding. In addition, the nitronate on the equatorial position may also possessed π–π stacking interaction with the nitrile group. Both of these could accelerate the cyclization process to form the key intermediate 6a. Finally, the 1,2-trans elimination of HCl gave the observed product 7aa. On the other hand, in TS-2, the hydrogen bonding network and the π–π stacking interaction were disrupted because of the distance between the nitronate and nitrile group. Moreover, the steric hindrance between the phenyl group and the nitronate also made this transition state unfavorable.

Recently, the enantioselective construction of axially chiral biaryls has attracted much attention, as their widely existence in natural products [48,49] and bioactive molecules [50–52], as well as in chiral ligands [53,54] and chiral organo-catalysts [55–57]. In this context, the successful synthesis of the ortho-brominated product 7ka encouraged us to test the possibility of the enantioselective synthesis of this stable atropisomer. With the proposed mechanism and the currently emerged “center-to-axial chirality transfer” strategy, the chirality in the first Michael addition step could transfer to the final axial chirality. Next, the commonly used bifunctional chiral organo-catalysts were used to introduce the chirality (Table 2). Interestingly, with quinine Cat. 1 as the catalyst, an intermediate was formed instead of the final product 7ka (Table 2, entry 1). Unfortunately, the intermediate was not stable during the separation process. Benefit from the results in Table 1, the addition of DBU promoted the intermediate to the final product 7ka in 70% yield and 17% ee. Considering the relatively weak basicity of quinine, the Michael adduct 9 was proposed to be the observed intermediate. This preliminary result promoted us to screen a series of cinchona alkaloid-derived catalysts to improve the enantioselectivity (Table 2, entries 2–8).
The well-defined bifunctional thiourea/urea Cat. 5-6 improved the enantioselectivities to 31% ee and 33% ee, respectively. Another bifunctional catalyst squaramide Cat. 7 further improved the ee to 40% (more details could be found in the Supplementary Materials), albeit with lower 40% yield (Table 2, entries 7). Extending the carbon chain of the 3,5-bis(trifluoromethyl)aniline moiety did not give better result (Table 2, entries 8). In addition, the replacement of cinchona alkaloid moiety with chiral cyclohexane diamine also failed to improve the ee (Table 2, entries 9–10). Next, with Cat. 7 as the catalyst, a quick survey of the solvent revealed that the ethyl acetate gave the best result, affording the product 7ka in 63% yield and 40% ee (Table 2, entries 14). Rather than the high-throughput screening of the reaction conditions, the chirality conversion efficiency from the intermediate 9 to the final product 7ka was essential for the enantioselectivity. Thus, in order to answer whether the relatively low ee was determined by the Michael addition step or by the chirality transfer step, the identification of the key intermediate 9 is still ongoing in our lab.

| ArClNO2 | NC-CN+ 1a 3a 7aa |
|---------|-------------------|
| 7aa, 95% | 7ba, 92% |
| 7ca, 85% |
| 7da, 81% |
| 7ea, 91% |
| 7fa, 97% |
| 7ga, 90% |
| 7ha, 97% |
| 7ia, 74% |
| 7ja, 75% |
| 7ka, 70% |
| 7la, 88% |
| 7ma, 88% |
| 7na, 87% |
| 7oa, 93% |
| 7pf, 88% |
| 7qa, 36% |
| 7ab, 80% |
| 7ac, 89% |
| 7ad, 89% |
| 7ae, 84% |
| 7af, 86% |
| 7ag, 68% |
| 7ah, 97% |
| 7ai, 13% |

Scheme 1. The scope of the substrates. 3 (0.2 mmol, 1.0 equiv), 1 (0.24 mmol, 1.2 equiv), and DBU (0.3 mmol, 1.5 equiv) were stirred at room temperature in toluene (2 mL).
Scheme 2. The proposed mechanism of the cyclization step. TS = transition state.

Table 2. The optimization of the chiral product.

| Entry | Cat. | Solvent | Yield (%) | Ee (%) |
|-------|------|---------|-----------|--------|
| 1     | Cat. 1 | DCM     | 70        | 17     |
| 2     | Cat. 2 | DCM     | 63        | -14    |
| 3     | Cat. 3 | DCM     | 71        | 23     |
| 4     | Cat. 4 | DCM     | 61        | 14     |
| 5     | Cat. 5 | DCM     | 65        | 31     |
| 6     | Cat. 6 | DCM     | 56        | 33     |
| 7     | Cat. 7 | DCM     | 40        | 40     |
| 8     | Cat. 8 | DCM     | 48        | 31     |
| 9     | Cat. 9 | DCM     | 48        | -31    |
| 10    | Cat. 10 | DCM    | 67        | -14    |
| 11    | Cat. 7 | DCE     | 38        | 37     |
| 12    | Cat. 7 | CHCl₃   | 35        | 39     |
| 13    | Cat. 7 | Toluene | 59        | 27     |
| 14    | Cat. 7 | EA      | 63        | 40     |

* Reaction conditions: 1a (0.10 mmol), 2q (0.12 mmol), catalyst Cat (10 mol %) were stirred in solvent (1.0 mL) for 12 h at room temperature. Next, DBU (0.1 mmol) was added.  

b Ee values were determined by chiral HPLC analysis.

3. Materials and Methods

The detailed procedure of the synthesis and characterization of the products are given in Supplementary Materials.

4. Conclusions

In conclusion, a facile Michael addition/cyclization/elimination cascade reaction between vinylogous malononitrile derivatives and chlorinated nitrostyrenes was developed to construct polysubstituted arenes. The method features the advantages of mild conditions, wide substrate scope, and high yield. Preliminary studies based on center-to-axial chirality transfer strategy revealed that chiral biaryl atropisomers could be obtained through the enantioselective version of this cascade reaction. Further investigation on the key intermediate of this reaction and the improvement of the enantioselectivity are still in progress in our lab.
Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27238167/s1. 1H and 13C NMR spectra for all compounds. References [13,58–60] are contained in the Supplementary Materials.

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References
1. Meyer, E.A.; Castellano, R.K.; Diederich, F. Interactions with aromatic rings in chemical and biological recognition. Angew. Chem. Int. Ed. 2003, 42, 1210–1250. [CrossRef] [PubMed]
2. Marson, C.M. New and unusual scaffolds in medicinal chemistry. Chem. Soc. Rev. 2011, 40, 5514–5533. [CrossRef] [PubMed]
3. Zhang, L.; Peng, X.; Danu, G.L.V.; Geng, R.; Zhou, C. Comprehensive review in current developments of imidazole-based medicinal chemistry. Med. Res. Rev. 2014, 34, 340–437. [CrossRef]
4. Tsutsu, L.S.; Gundisch, D.; Sun, D. Carbazole scaffold in medicinal chemistry and natural products: A review from 2010–2015. Curr. Top. Med. Chem. 2016, 16, 1290–1313. [CrossRef] [PubMed]
5. Gromov, S.P.; Dmitrieva, S.N.; Vedernikov, A.I.; Churakova, M.V. Phenylaza- and benzoazacrown compounds with a nitrogen atom conjugated with a benzene ring. Russ. Chem. Rev. 2005, 74, 461–488. [CrossRef]
6. Yamamoto, K.; Sugawa, T.; Murahashi, T. Multinuclear coordination of fused benzene ring hydrocarbons. Coord. Chem. Rev. 2022, 466, 214575. [CrossRef]
7. Subbiah, M.A.M.; Meanwell, N.A. Bioisosteres of the phenyl ring: Recent strategic applications in lead optimization and drug design. J. Med. Chem. 2021, 64, 14046–14128. [CrossRef]
8. Sharma, P.C.; Sinhm, A.; Sharma, A.; Rajak, H.; Pathak, D.P. Medicinal significance of benzothiazole scaffold: An insight view. J. Enzyme. Inhib. Med. Chem. 2013, 28, 240–266. [CrossRef]
9. Corbet, J.-P.; Mignani, G. Selected patented cross-coupling reaction technologies. Chem. Rev. 2006, 106, 2651–2710. [CrossRef]
10. Ashenhurst, J.A. Intermolecular oxidative cross-coupling of arenes. Chem. Soc. Rev. 2010, 39, 540–548. [CrossRef]
11. Kozlowski, M.C.; Morgana, B.J.; Lintona, E.C. Total synthesis of chiral biaryl natural products by asymmetric biaryl coupling. Chem. Soc. Rev. 2009, 38, 3193–3207. [CrossRef]
12. Bringmann, G.; Gulder, T.; Gulder, T.A.M.; Breuning, M. Atroposelective total synthesis of axially chiral biaryl natural products. Chem. Rev. 2011, 111, 563–639. [CrossRef]
13. Bauvois, B.; Puiffo, M.-L.; Bongui, J.-B.; Paillet, S.; Monneret, C.; Dauzzonne, D. Synthesis and biological evaluation of novel flavone-8-acid derivatives as reversible inhibitors of aminopeptidase N/CD13. J. Med. Chem. 2003, 46, 3900–3913. [CrossRef]
14. Ni, Q.; Wang, X.; Zeng, D.; Wu, Q.; Song, X. Organocatalytic asymmetric synthesis of aza-spirooxindoles via michael/friedel-crafts cascade reaction of 1,3,5-ti-nitroenynes and 3-pyrollyloxindoles. Org. Lett. 2021, 23, 2273–2278. [CrossRef]
15. Raut, V.S.; Jean, M.; Vanthuyne, N.; Roussel, C.; Constantieux, T.; Bressy, C.; Bugaut, X.; Bonne, D.; Rodriguez, J. Enantioselective syntheses of furan atropisomers by an oxidative central-to-axial chirality conversion strategy. J. Am. Chem. Soc. 2017, 139, 2140–2143. [CrossRef]
16. Mane, V.; Sivandan, S.T.; Santana, R.G.; Beatriz, A.; Junior, E.N.S.; Namboothiri, I.N.N. Synthesis of densely substituted sulfonylfurans and dihydrofurans via cascade reactions of α-functionalized nitroalkenes with β-ketosulfones. J. Org. Chem. 2020, 85, 8825–8843. [CrossRef]
17. Feng, J.; Wang, S.; Feng, J.; Li, Q.; Yue, J.; Yue, G.; Zou, P.; Wang, G. Mild and efficient synthesis of trans-3-aryl-2-nitro-2,3-dihydrobenzofurans on water. New J. Chem. 2020, 44, 11937–11940. [CrossRef]
44. George, N.; Akhtar, M.J.; Balushi, K.A.A.; Khan, S.A. Rational drug design strategies for the development of promising multi-target directed indole hybrids as anti-alzheimer agents. *Bioorg. Chem.* 2022, 127, 105941. [CrossRef] [PubMed]

45. Hong, Y.; Zhu, Y.-Y.; He, Q.; Gu, S.-X. Indole derivatives as tubulin polymerization inhibitors for the development of promising anticancer agents. *Bioorg. Med. Chem.* 2021, 55, 116597. [CrossRef] [PubMed]

46. Goyal, D.; Kaur, A.; Goyal, B. Benzofuran and indole: Promising scaffolds for drug development in alzheimer’s disease. *ChemMedChem* 2018, 13, 1275–1299. [CrossRef]

47. Lunagariya, J.; Bhadja, P.; Zhong, S.; Vekariya, R.; Xu, S. Marine natural product bis-indole alkaloid caulerpin: Chemistry and biology. *Mini. Rev. Med. Chem.* 2019, 19, 751–761. [CrossRef]

48. Bringmann, G.; Mortimer, A.J.P.; Keller, P.A.; Gresser, M.J.; Garner, J.; Breuning, M. Atroposelective synthesis of axially chiral biaryl compounds. *Angew. Chem. Int. Ed.* 2005, 44, 5384–5427. [CrossRef]

49. Delord, J.W.; Panossian, A.; Leroux, F.R.; Colobert, F. Recent advances and new concepts for the synthesis of axially stereoenriched biaryls. *Chem. Soc. Rev.* 2015, 44, 3418–3430. [CrossRef]

50. Wang, Z.; Meng, L.; Liu, X.; Zhang, L.; Yu, Z.; Wu, G. Recent progress toward developing axial chirality bioactive compounds. *Eur. J. Med. Chem.* 2022, 243, 114700. [CrossRef]

51. Huettel, W.; Mueller, M. Regio- and stereoselective intermolecular phenol coupling enzymes in secondary metabolite biosynthesis. *Nat. Prod. Rep.* 2021, 38, 1011–1043. [CrossRef]

52. Carlsson, A.-C.C.; Karlsson, S.; Munday, R.H.; Tatton, M.R. Approaches to Synthesis and Isolation of Enantiomerically Pure Biologically Active Atropisomers. *Acc. Chem. Res.* 2022, 55, 2938–2948. [CrossRef]

53. Li, Y.-M.; Kwong, F.-Y.; Yu, W.-Y.; Chan, A.S.C. Recent advances in developing new axially chiral phosphine ligands for asymmetric catalysis. *Coord. Chem. Rev.* 2007, 257, 2119–2144. [CrossRef]

54. Mancinelli, M.; Bencivenni, G.; Pecorari, D.; Mazzanti, A. Stereochemistry and recent applications of axially chiral organic molecules. *Eur. J. Org. Chem.* 2020, 2020, 4070–4086. [CrossRef]

55. Shirakawa, S.; Liu, S.; Kaneko, S. Organocatalyzed asymmetric synthesis of axially, planar, and helical chiral compounds. *Chem. Asian J.* 2016, 11, 330–341. [CrossRef]

56. Bonne, D.; Rodriguez, J. Enantioselective syntheses of atropisomers featuring a five-membered ring. *Chem. Commun.* 2017, 53, 12385–12393. [CrossRef]

57. Bai, X.-F.; Cui, Y.-M.; Cao, J.; Xu, L.-W. Atropisomers with axial and point chirality: Synthesis and applications. *Acc. Chem. Res.* 2022, 55, 2545–2561. [CrossRef]

58. Pan, H.; Han, M.-Y.; Li, P.; Wang, L. “On Water” Direct Catalytic Vinylogous Aldol Reaction of Silyl Glyoxylates. *J. Org. Chem.* 2019, 84(21), 14281–14290. [CrossRef]

59. Yang, W.; Du, D.-M. Highly enantioselective Michael addition of nitroalkanes to chalcones using chiral squaramides as hydrogen bonding organocatalysts. *Org. Lett.* 2010, 12, 5450–5453. [CrossRef]

60. Requena, J.V.A.; Lopez, E.M.; Herrera, R.P. One-pot synthesis of unsymmetrical squaramides. *RSC Adv.* 2015, 5, 33450–33462. [CrossRef]