A convenient three-component reaction leading to the synthesis of polysubstituted cyclohexene derivatives†

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A three-component reaction of β-nitrostyrene, arylmethylidenemalononitrile and malononitrile catalyzed by imidazole produced the corresponding polysubstituted cyclohexene derivatives in moderate to good yields under mild conditions. A further improvement of this three-component reaction has also been achieved by starting from a commercially available aromatic aldehyde, nitromethane and malononitrile to give the products in moderate yields.

Introduction

One-pot and multi-component reactions are particularly effective at building functionalized, drug-like structures from different families of compounds in a single step. Thus far, one-pot and multi-component reactions have already come quite close to the idea of an "ideal synthesis".[1] Among the employed reactants, malononitrile ($pK_a = 11.2$), activated by the strongly electron-withdrawing cyano groups, is an extremely useful compound in this context and is therefore used widely as a reactant or reaction intermediate.[2,3] Moreover, the unique reactive nature of methylenemalononitrile [$R^1R^2C{=}C(CN)_2$] in the presence of base has also been known for some time.[4] In particular, the tendency of such compounds to undergo condensations and dimerizations in the presence of base has been the subject of several interesting investigations during the last several decades.[5]

In recent years, the condensation reactions of malononitrile or methylenemalononitrile as one component have been reported widely. For example, Adib *et al.* developed a one-pot, three-component reaction between arylmethylidenemalononitriles, dialkylacetylenedicarboxylates, and malononitrile, affording highly substituted benzene derivatives in good to excellent yields.[6] Texier-Boullet has reported a new route to functionalized cyclohexenes under solvent-free conditions catalyzed by piperidine upon microwave irradiation from electrophilic alkenes activated by cyano and methoxycarbonyl groups and nitromethane.[7,8] Moreover, Wang *et al.* also synthesized a series of 2-amino-1,3,3-tricyano-5-nitro-4,6-diarylcyclohexenes **4** (their relative configurations have been assigned as those of diastereoisomers **4-3** in this paper) by reaction of arylmethylidenemalononitriles and nitromethane catalyzed by KF-alumina.[9] In this paper, we wish to report our method to synthesize polysubstituted cyclohexene derivatives **4** in a three-component and one-pot manner in moderate to good yields and moderate diastereoselectivities in the presence of imidazole (50 mol%) (products **4-1** have been assigned as the major diastereoisomers). Moreover, the stereochemistry of these diastereoisomers has been clarified in this paper.

Results and discussion

When a mixture of β-nitrostyrene **1a**, benzylidenemalononitrile **2a**, malononitrile **3** and a catalytic amount of imidazole was stirred in dichloromethane (DCM) for several hours, polysubstituted cyclohexene derivative **4a** was isolated as diastereoisomeric mixtures by column chromatography on silica gel. A survey of some reaction parameters was performed, and some representative results are summarized in Tables 1 and 2, respectively. Upon examination of a variety of nitrogen-containing Lewis bases and phosphorus-containing Lewis bases, we found that nitrogen-containing Lewis bases such as imidazole, 1-methylimidazole and 1,4-diazabicyclo[2.2.2]octane (DABCO) (50 mol%) are more efficient catalysts than others and phosphorus-containing Lewis bases, providing **4a** in 85%, 73%, and 81% yields, respectively after 24 h (Table 1, entries 2, 5 and 9), although during a short reaction time, **4a** was produced in lower yields (Table 1, entries 1 and 4). Using 20 mol% of nitrogen-containing Lewis bases as the catalysts afforded **4a** in similar yields under identical conditions (Table 1, entries 3 and 6). Pyridine and 2,6-lutidine could provide **4a** in 41% and 69% yields under the standard conditions, respectively (Table 1, entries 13 and 14). However, *N*,*N*-4-dimethylaminopyridine (DMAP) could not efficiently catalyse this reaction, affording only trace amount of **4a** under otherwise identical conditions (Table 1, entry 15). It should be also noted that different bases produced **4a** in different dr values. Using imidazole as the catalyst afforded **4a-1** as the major diastereoisomer along with minor diastereoisomers of **4a-1** and **4a-2**. When 1-methylimidazole or benzimidazole was used as the catalyst, **4a-2** was produced as the major diastereoisomer (Table 1, entries 4–6 and 8). Moreover, we found that phosphorus-containing Lewis bases such as PPh_3, PBu_3 and PPh_2Me (50 mol%) could also catalyse the reaction under similar conditions to afford **4a-3** as the major diastereoisomer in some cases, although the total yields of **4a** were low (Table 1, entries 16–18). The control experiment revealed that no reaction occurred in the absence of any base (Table 1, entry 19).

The relative configurations of **4a-1** and **4a-2** have been unambiguously determined by X-ray crystal diffraction (ESI†)[10] and the

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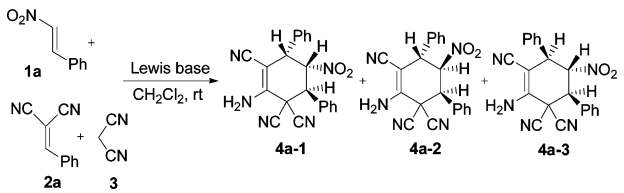
† Electronic supplementary information (ESI) available: ^1H NMR and ^{13}C spectroscopic and analytical data for **4**, X-ray crystal structures of **4a-1** and **4a-2**, and a detailed description of the experimental procedure. CCDC reference numbers 688759 and 688760. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810299f

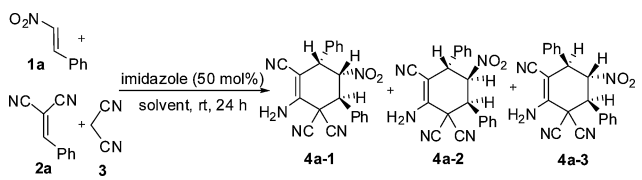
Table 1 Survey of Lewis base for the three-component reaction of β-nitrostyrene **1a**, benzylidenemalononitrile **2a** and malononitrile **3**



Entry[a]	Lewis base	Time	Yield[b](%) **4a**	dr[c] **4a-1** : **4a-2** : **4a-3**
1	Imidazole (50 mol%)	6 h	67	71 : 16 : 13
2	Imidazole (50 mol%)	24 h	85	71 : 16 : 13
3	***Imidazole (20 mol%)***	***24 h***	**82**	***71 : 16 : 13***
4	1-Methylimidazole (50 mol%)	6 h	62	40 : 46 : 14
5	1-Methylimidazole (50 mol%)	24 h	73	40 : 46 : 14
6	1-Methylimidazole (20 mol%)	24 h	81	40 : 46 : 14
7	Pyrazole (50 mol%)	24 h	30	75 : 16 : 9
8	Benzimidazole (50 mol%)	24 h	55	36 : 50 : 14
9	DABCO (50 mol%)	24 h	81	77 : 11 : 12
10	NEt_3 (50 mol%)	10 min	47	80 : 12 : 8
11	DBU (50 mol%)	10 min	45	53 : 10 : 37
12[d]	DBU (50 mol%)	10 min	32	53 : 10 : 37
13	Pyridine (50 mol%)	24 h	41	69 : 23 : 8
14	2,6-Lutidine (50 mol%)	24 h	69	74 : 20 : 6
15	DMAP (50 mol%)	24 h	Trace	—
16	PPh_3 (50 mol%)	24 h	57	48 : 9 : 43
17	PBu_3 (50mol%)	24 h	36	26 : 1 : 73
18	PPh_2Me (50 mol%)	24 h	30	6 : 0 : 94
19	—	24 h	NR	—

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), **3** (0.2 mmol) and Lewis base in CH_2CI_2 (0.5 mL). [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopic data. [d] This reaction was carried out at −10 °C.

Table 2 Survey of solvent effects for the three-component reaction of β-nitrostyrene **1a**, benzylidene-malononitrile **2a** and malononitrile **3**



Entry[a]	Solvent	Yield[b] (%) **4a**	dr[c] **4a-1** : **4a-2** : **4a-3**
1	CH_3CN	68	52 : 12 : 36
2	THF	80	74 : 19 : 7
3	DCE	64	71 : 18 : 11
4	Toluene	46	70 : 12 : 18
5	Dioxane	64	50 : 39 : 11
6	Et_2O	78	61 : 24 : 15
7	CH_3OH	41	56 : 10 : 34
8	DMF	43	18 : 4 : 78

[a] All reactions were carried out with **1a** (0.2 mmol), **2a** (0.2 mmol), **3** (0.2 mmol) and imidazole (0.1 mmol) in solvents (0.5 mL). [b] Isolated yields. [c] Determined by ^{1}H NMR spectroscopic data.

relative configuration of **4a-3** was determined by comparing the ^{1}H NMR spectroscopic data with those of literature data.[9]

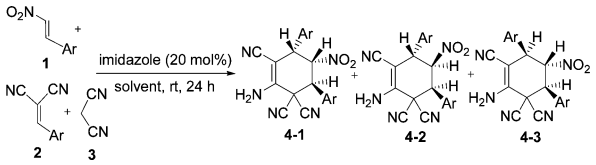
The examination of solvent effects revealed that DCM, tetrahydrofuran (THF) and ether (Et_2O) are the suitable solvents to give **4a** in higher yields and **4a-1** as the major diastereoisomer in the presence of 50 mol% of imidazole (Table 1, entry 2 and Table 2, entries 2 and 6). The employed solvent could also affect the distribution of these diastereoisomers. For example, in DMF, **4a-3** was obtained as the major diastereoisomer using imidazole as the catalyst (Table 2, entry 8).

Under these optimized reaction conditions, we then utilized 20 mol% of imidazole as the catalyst and DCM as the solvent to examine the scope and limitations of this reaction with a variety of **1** and **2** bearing different types of substituents on the benzene rings and the results of these experiments are summarized in Table 3. As shown in Table 3, this three-component reaction displays a broad scope. Whatever electron-withdrawing or electron-donating substituent was introduced at the *ortho*, *meta* or *para* position of the benzene rings of **1** and **2**, the products **4** were obtained in good yields with products **4-1** as the major diastereoisomers.

Under these optimized reaction conditions, we also examined the three-component reaction in which the substituents on the benzene rings of β-nitroalkene **1** and arylmethylidenemalononitrile **2** are different. Unfortunately, complex product mixtures were formed on the basis of ^{1}H NMR spectroscopic investigation under identical conditions, suggesting that an aromatic group exchange process exists between nitroalkene and arylmethylidenemalononitrile (Scheme 1). The additional and detailed information on the exchange of aromatic groups can be found in the ESI.†

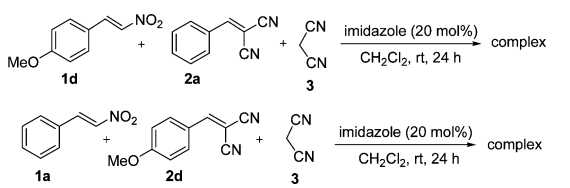
A plausible reaction mechanism is shown in Scheme 2 on the basis of previous literature. Two possible initiation processes exist. In path A, the first step is the nucleophilic attack of nitrogen-containing Lewis bases or phosphorus-containing Lewis bases

Table 3 Scope of the three-component reaction of nitroalkene **1**, arylmethylidenemalononitrile **2** and malononitrile **3**



Entry[a]	Ar	Yield[b] (%) 4-1	dr[c] 4-1 : 4-2 : 4-3
1	*p*-ClC_6H_4 **1b**	**4b**, 69	70 : 20 : 10
2	*p*-MeC_6H_4 **1c**	**4c**, 69	72 : 24 : 4
3	*p*-$MeOC_6H$ **1d**	**4d**, 63	70 : 19 : 11
4	*p*-FC_6H **1e**	**4e**, 64	65 : 21 : 14
5	*m*-MeC_6H_4 **1f**	**4f**, 78	70 : 27 : 3
6	*m*-BrC_6H_4 **1g**	**4g**, 60	66 : 24 : 10
7	*m*-FC_6H **1h**	**4h**, 72	86 : 9 : 5
8	*o*-BrC_6H **1i**	**4i**, 78	—[d]
9	*o*-ClC_6H_4 **1j**	**4J**, 61	—[d]

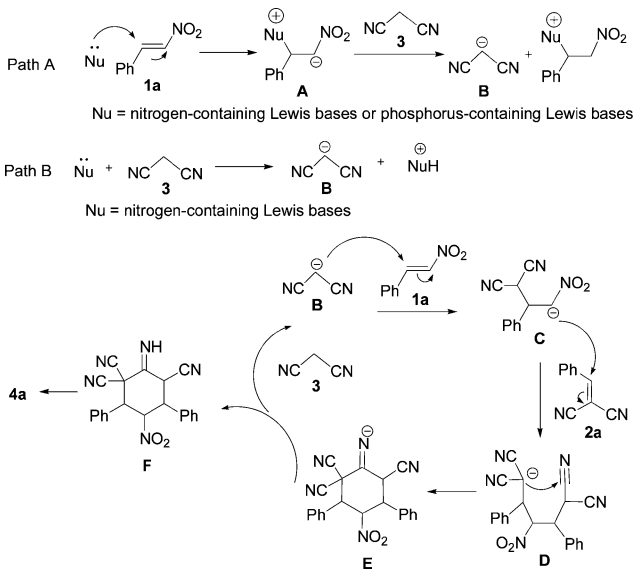
[a] All reactions were carried out with **1** (0.4 mmol), **2** (0.4 mmol), **3** (0.4 mmol) and imidazole (0.08 mmol) in CH_2Cl_2 (1.0 mL). [b] Isolated yields. [c] Determined by ^1H NMR spectroscopic data. [d] Compounds **4i-1** and **4j-1** are the major diastereoisomers. It is hard to determine the dr values of **4-2** and **4-3** because the proton signals overlap in their ^1H NMR spectra.



Scheme 1 The three-component reaction in which the substituents on the benzene rings of nitroalkene and arylmethylidenemalononitrile are different.

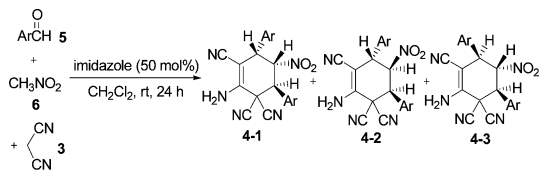
to β-nitrostyrene **1a** to generate zwitterionic intermediate **A**, which abstracts a proton from malononitrile **3** to give anionic intermediate **B**. In path B, the nitrogen-containing Lewis bases directly deprive malononitrile **3** of a proton to give anionic intermediate **B**. The subsequent process in path A and B is the same after producing **B**. The nucleophilic attack of intermediate **B** to **1a** produces intermediate **C**, which can give intermediate **D** *via* another intermolecular nucleophilic attack with benzylidenemalononitrile **2a**. The intramolecular nucleophilic addition of the newly formed anion to one nitrile group produces the six-membered intermediate **E**. The nitrogen anion in intermediate **E** abstracts a proton from malononitrile **3** to provide intermediate **F** and regenerates the anionic intermediate **B**. The tautomerization of intermediate **F** furnishes the final product **4a** (Scheme 2). The generation of anionic intermediate **B** is the key step to initiate this three-component tandem reaction.

In this three-component reaction, the substrates β-nitrostyrene **1a** and benzylidenemalononitrile **2a** were prepared from the reaction of benzaldehyde with nitromethane and malononitrile, respectively. Therefore, we envisaged that this reaction could also be conducted using benzaldehyde, nitromethane and malononitrile since β-nitrostyrene **1a** and benzylidenemalononitrile **2a** can be formed *in situ* under the optimized reaction conditions. At first, the reaction was conducted with arylaldehyde,



Scheme 2 A plausible reaction mechanism.

Table 4 Three-component reaction of aromatic aldehyde **5**, nitromethane **6** and malononitrile **3**



Entry	Ar	Yield[e] (%) 4	dr[d] 4-1 : 4-2 : 4-3
1[a]	C_6H_5	**4a**, 34	70 : 25 : 5
2[a]	*p*-ClC_6H_4	**4b**, 37	70 : 15 : 15
3[a]	*m*-MeC_6H_4	**4f**, 43	74 : 19 : 7
4[b]	C_6H_5	**4a**, 70	70 : 23 : 7
5[b]	*p*-ClC_6H_4	**4b**, 49	62 : 15 : 23
6[b]	*m*-MeC_6H_4	**4f**, 74	71 : 20 : 9
7[b]	*p*-FC_6H_4	**4e**, 65	68 : 19 : 13
8[b]	*o*-ClC_6H_4	**4j**, 65	—[e]

[a] These reactions were carried out with **5** (0.8 mmol), **6** (0.4 mmol), **3** (0.8 mmol) and imidazole (0.2 mmol) in CH_2Cl_2 (1.0 mL). [b] These reactions were carried out with **5** (0.8 mmol), **6** (1.2 mmol), **3** (0.8 mmol) and imidazole (0.2 mmol) in CH_2Cl_2 (1.0 mL). [c] Isolated yields. [d] Determined by ^1H NMR spectroscopic data. [e] Compound **4j-1** is the major diastereoisomer. It is difficult to determine the dr values of **4j-2** and **4j-3** because the proton signals overlap in the ^1H NMR spectrum.

nitromethane and malononitrile in a ratio of 2 : 1 : 2 in DCM in the presence of imidazole (50 mol%), but the corresponding products **4** were obtained in low yields and the corresponding arylmethylidenemalononitriles could be isolated as byproducts (Table 4, entries 1, 2 and 3). A control experiment was performed by using benzylidenemalononitrile (1.0 equiv) and nitromethane (1.5 equiv), affording **4a** in 50% yield. This result suggests that the employed amount of nitromethane is crucial for the yield of **4a**. Increasing the amount of nitromethane with the ratio of benzaldehyde, nitromethane and malononitrile as 2 : 3 : 2 afforded the corresponding products **4** in good yields for a variety of arylaldehydes (Table 4, entries 4–8).

In conclusion, we have disclosed a convenient three-component reaction of β-nitrostyrene, arylmethylidenemalononitrile and malononitrile catalyzed by imidazole leading to the synthesis of polysubstituted cyclohexene derivatives in good yields with products **4-1** as the major diastereoisomers under mild conditions. Moreover, this reaction can be conducted with commercially available aromatic aldehyde, nitromethane and malononitrile to produce the polysubstituted cyclohexene derivatives in moderate yields. The employed Lewis bases and solvents can significantly affect the configuration of the products. Efforts are in progress to elucidate further mechanistic details of these reactions and to understand their scope and limitations.

Experimental section

General remarks

All solvents were purified by distillation. Unless otherwise stated, all reactions were carried out under an argon atmosphere. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer as a solution in $CDCl_3$ or CD_3COCD_3 with tetramethylsilane (TMS) as an internal standard; *J* values are in Hz. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. Infrared spectra were measured on a Perkin-Elmer 983 spectrometer. MPs were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure.

General procedure for the reaction of β-nitrostyrene 1a, benzylidenemalononitrile 2a, and malononitrile 3

β-Nitrostyrene **1a** (30 mg, 0.2 mmol), benzylidenemalononitrile **2a** (31 mg, 0.2 mmol), malononitrile **3** (13 mg, 0.2 mmol) and imidazole (7 mg, 0.1 mmol) were stirred in CH_2Cl_2 (0.5 mL) in a 10 mL Schlenk tube. After the reaction mixture was stirred at 20 °C for 24 hours, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, eluent: EtOAc–petroleum ether = 1 : 6) to yield the corresponding product **4** as a white powder. After careful recrystallization in EtOH, the major diastereoisomer **4a-1** was obtained.

General procedure for the reaction of benzaldehyde 5a, nitromethane 6 and malononitrile 3

Benzaldehyde **5a** (85 mg, 0.8 mmol), nitromethane **6** (73 mg, 1.2 mmol), malononitrile **3** (53 mg, 0.8 mmol) and imidazole (14 mg, 0.2 mmol) were stirred in CH_2Cl_2 (1.0 mL) in a 10 mL Schlenk tube. After the reaction mixture was stirred at 20 °C for 24 hours, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (SiO_2, eluent: EtOAc–petroleum ether = 1 : 6) to yield the corresponding product **4** as a white powder.

Compound 4a-1. A white solid, mp: 167–169 °C. ^{1}H NMR (CD_3COCD_3, 300 MHz, TMS) δ 4.44 (d, 1H, J = 10.2 Hz, CH), 5.10 (d, 1H, J = 4.5 Hz, CH), 5.51 (dd, 1H, J_1 = 10.2 Hz, J_2 = 4.5 Hz, CH), 6.96 (s, 2H, NH_2), 7.36–7.55 (m, 10H, Ar); ^{13}C NMR (CD_3COCD_3, 75 MHz, TMS) δ 40.9, 41.4, 50.2, 81.5, 87.3, 111.1, 114.0, 116.3, 129.3, 129.5, 129.8, 130.2, 131.0, 131.1, 138.1, 144.9; IR (CH_2Cl_2): ν 3423, 3358, 3230, 2208, 1650, 1616, 1562, 1495, 1456, 1363, 781, 757, 736, 700 cm^{-1}; MS (EI) *m/z* (%): 369 [M$^+$] (0.7), 322 (24.5), 321 (18.2), 245 (22.2), 207 (17.3), 206 (100), 25 (18.5), 91 (18.9), 77 (21.9); HRMS (EI) Calcd. for $C_{21}H_{15}N_5O_2$ (M$^+$) requires 369.1226, Found: 369.1214.

Compound 4a-2. A white solid, mp: 162–164 °C. ^{1}H NMR (CD_3COCD_3, 300 MHz, TMS) δ 4.40 (d, 1H, J = 12.9 Hz, CH), 4.77 (d, 1H, J = 6.3 Hz, CH), 6.24 (dd, 1H, J_1 = 12.9 Hz, J_2 = 6.3 Hz, CH), 6.94 (s, 2H, NH_2), 7.34–7.51 (m, 8H, Ar), 7.60–7.63 (m, 2H, Ar); ^{13}C NMR (CD_3COCD_3, 75 MHz, TMS) δ 43.8, 44.3, 44.9, 79.4, 83.9, 111.8, 112.2, 117.0, 129.57, 129.6, 129.7, 130.4, 133.0, 135.5, 145.4; IR (CH_2Cl_2): ν 3447, 3360, 3225, 3034, 2208, 1650, 1621, 1562, 1493, 1455, 1361, 754, 738, 703 cm^{-1}; MS (EI) *m/z* (%): 369 [M$^+$] (14.3), 323 (17.8), 322 (21.2), 221 (21.6), 220 (100), 219 (20.6), 194 (29.6), 193 (32.9), 91 (31.5); HRMS (EI) Calcd. for $C_{21}H_{15}N_5O_2$ (M$^+$) requires 369.1226, Found: 369.1216.

Compound 4b-1. A white solid, mp: 166–168 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 3.91 (d, 1H, J = 12.6 Hz, CH), 4.53 (d, 1H, J = 6.3 Hz, CH), 5.26 (s, 2H, NH_2), 5.61 (dd, 1H, J_1 = 12.6 Hz, J_2 = 6.3 Hz, CH), 7.06 (d, 2H, J = 8.4 Hz, Ar), 7.29 (d, 2H, J = 8.4 Hz, Ar), 7.39–7.44 (m, 4H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 42.8, 43.2, 43.3, 80.3, 82.7, 110.3, 110.7, 115.4, 128.8, 129.0, 129.6, 129.9, 130.0, 131.2, 136.2, 136.9, 143.9; IR (CH_2Cl_2): ν 3453, 3359, 3226, 2924, 2853, 2209, 1649, 1619, 1563, 1493, 1414, 1359, 1095, 1014, 835, 740 cm^{-1}; MS (EI) *m/z* (%): 437 [M$^+$] (2.4), 256 (34.9), 255 (17.9), 254 (100), 240 (19.0), 228 (9.3), 219 (41.1), 127 (8.9), 125 (20.7); HRMS (EI) Calcd. for $C_{21}H_{13}Cl_2N_5O_2$ (M$^+$) requires 437.0446, Found: 437.0446.

Compound 4c-1. A white solid, mp: 170–172 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.32 (s, 3H, CH_3), 2.34 (s, 3H, CH_3), 3.96 (d, 1H, J = 12.3 Hz, CH), 4.49 (d, 1H, J = 6.3 Hz, CH), 5.17 (s, 2H, NH_2), 5.63 (dd, 1H, J_1 = 12.3 Hz, J_2 = 6.3 Hz, CH), 6.99 (d, 2H, J = 8.1 Hz, Ar), 7.20 (d, 4H, J = 8.7 Hz, Ar), 7.27 (d, 2H, J = 8.1 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.11, 21.14, 43.3, 43.5, 43.6, 81.3, 83.0, 110.7, 111.1, 115.7, 127.6, 128.2, 129.8, 130.2, 139.8, 140.5, 143.6; IR (CH_2Cl_2): ν 3446, 3359, 3229, 2923, 2207, 1648, 1615, 1562, 1515, 1362, 826, 739, 720 cm^{-1}; MS (EI) *m/z* (%): 397 [M$^+$] (4.3), 259 (13.6), 234 (100), 220 (29.3), 219 (46.0), 208 (19.7), 115 (13.4), 128 (24.0), 105 (23.3); HRMS (EI) Calcd. for $C_{23}H_{19}N_5O_2$ (M$^+$) requires 397.1539, Found: 397.1534.

Compound 4d-1. A white solid, mp: 150–152 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 3.78 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 3.93 (d, 1H, J = 12.6 Hz, CH), 4.48 (d, 1H, J = 6.0 Hz, CH), 5.16 (s, 2H, NH_2), 5.59 (dd, 1H, J_1 = 12.6 Hz, J_2 = 6.0 Hz, CH), 6.92 (d, 4H, J = 8.4 Hz, Ar), 7.03 (d, 2H, J = 8.4 Hz, Ar), 7.32 (d, 2H, J = 8.4 Hz, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 43.2, 43.37, 43.42, 55.3, 81.5, 83.2, 110.8, 111.2, 114.87, 114.92, 115.7, 122.4, 124.6, 129.6, 143.4, 160.6, 160.9; IR (CH_2Cl_2): ν 3452, 3355, 3228, 3304, 2960, 2930, 2840, 2208, 2047, 1894, 1707, 1651, 1610, 1562, 1514, 1361, 1255, 1180, 1030, 837, 738 cm^{-1}; MS (EI) *m/z* (%): 429 [M$^+$] (13.4), 251 (17.6), 250 (100), 236 (21.5), 224 (31.5), 179 (47.4), 132 (27.1), 121 (27.0); HRMS (EI) Calcd. for $C_{23}H_{19}N_5O_4$ (M$^+$) requires 429.1437, Found: 429.1436.

Compound 4e-1. A white solid, mp: 215–217 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 3.94 (d, 1H, J = 12.9 Hz, CH), 4.54 (d, 1H, J = 6.0 Hz, CH), 5.31 (s, 2H, NH_2), 5.61 (dd, 1H, J_1 = 12.9 Hz, J_2 = 6.0 Hz, CH), 7.10–7.16 (m, 6H, Ar), 7.38–7.42 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 42.9, 43.0, 43.2, 80.7, 82.9, 110.4, 110.8, 115.5, 116.8 (d, J = 21.8 Hz), 116.9 (d, J = 21.8 Hz), 126.2, 126.3, 128.5, 128.6, 130.1 (d, J = 8.6 Hz), 143.7, 163.5 (d, J = 249 Hz), 163.7 (d, J = 250.2 Hz); IR (CH_2Cl_2): ν 3452, 3359, 3229, 2917, 2208, 1651, 1606, 1563, 1511, 1361, 1233, 1164, 842, 808, 739, 526 cm^{-1}; MS (EI) m/z (%): 405 [M$^+$] (3.7), 239 (16.5), 238 (100), 237 (13.6), 224 (18.6), 212 (22.6), 211 (14.7), 133 (8.9), 109 (30.5); HRMS (EI) Calcd. for $C_{21}H_{13}F_2N_5O_2$ (M$^+$) requires 405.1037, Found: 405.1049.

Compound 4f-1. A white solid, mp: 196–198 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 3.96 (d, 1H, J = 12.9 Hz, CH), 4.48 (d, 1H, J = 6.0 Hz, CH), 5.19 (s, 2H, NH_2), 5.64 (dd, 1H, J_1 = 12.9 Hz, J_2 = 6.0 Hz, CH), 6.88 (s, 1H, Ar), 6.92 (d, 1H, J = 7.8 Hz, Ar), 7.19–7.24 (m, 4H, Ar), 7.27–7.32 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 21.4, 21.5, 43.2, 43.7, 43.9, 81.3, 83.0, 110.6, 111.1, 115.7, 125.4, 129.1, 129.3, 129.4, 130.6, 130.7, 131.2, 132.7, 139.4, 139.5, 143.7; IR (CH_2Cl_2): ν 3453, 3359, 3230, 3026, 2922, 2208, 1650, 1563, 1358, 739, 709 cm^{-1}; MS (EI) m/z (%): 397 [M$^+$] (8.0), 351 (33.2), 350 (45.3), 259 (35.8), 234 (100), 220 (33.3), 219 (43.9), 208 (26.0), 105 (27.8); HRMS (EI) Calcd. for $C_{23}H_{19}N_5O_2$ (M$^+$) requires 397.1539, Found: 397.1539.

Compound 4g-1. A white solid, mp: 215–217 °C. ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 3.92 (d, 1H, J = 12.6 Hz, CH), 4.52 (d, 1H, J = 6.3 Hz, CH), 5.39 (s, 2H, NH_2), 5.62 (dd, 1H, J_1 = 12.6 Hz, J_2 = 6.3 Hz, CH), 7.06 (d, 1H, J = 7.8 Hz, Ar), 7.26–7.37 (m, 4H, Ar), 7.56–7.61 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 42.7, 43.27, 43.33, 80.2, 82.5, 110.2, 110.5, 115.3, 123.6, 123.7, 127.1, 131.1, 131.15, 131.2, 132.5, 133.3, 133.9, 134.9, 143.8; IR (CH_2Cl_2): ν 3451, 3359, 3225, 3061, 2973, 2208, 1650, 1562, 1477, 1431, 1358, 1076, 997, 780, 738, 708, 691 cm^{-1}; MS (EI) m/z (%): 525 [M$^+$] (9.1), 481 (32.2), 300 (94.4), 298 (100), 286 (41.1), 284 (41.4), 271 (27.9), 219 (80.1), 102 (25.5); HRMS (EI) Calcd. for $C_{21}H_{13}Br_2N_5O_2$ (M$^+$) requires 524.9436, Found: 524.9423.

Compound 4h-1. A white solid, mp: 275–277 °C. ^{1}H NMR (CD_3COCD_3, 300 MHz, TMS) δ 4.62 (d, 1H, J = 12.3 Hz, CH), 4.86 (d, 1H, J = 6.6 Hz, CH), 6.29 (dd, 1H, J_1 = 12.3 Hz, J_2 = 6.6 Hz, CH), 7.01 (s, 2H, NH_2), 7.15–7.30 (m, 4H, Ar), 7.41–7.59 (m, 4H, Ar); ^{13}C NMR (CD_3COCD_3, 75 MHz, TMS) δ 43.4, 43.5 (d, J = 1.7 Hz), 44.2 (d, J = 1.7 Hz), 78.8, 83.8, 111.6, 111.7, 116.5 (d, J = 28.6 Hz), 116.592 (d, J = 28.6 Hz), 116.597, 117.2, 117.5, 125.69, 125.72, 131.4 (d, J = 9.2 Hz), 131.7 (d, J = 8.0 Hz), 135.5 (d, J = 7.7 Hz), 138.2 (d, J = 6.8 Hz), 145.6, 163.1 (d, J = 245.0 Hz), 163.4 (d, J = 244.1 Hz); IR (CH_2Cl_2): ν 3400, 3340, 3237, 2920, 2207, 1658, 1612, 1566, 1488, 1449, 1363, 1222, 1151, 782, 755, 704 cm^{-1}; MS (EI) m/z (%): 405 [M$^+$] (24.4), 359 (53.9), 358 (42.1), 357 (31.5), 263 (41.5), 239 (33.0), 238 (100), 224 (48.0), 211 (53.2); HRMS (EI) Calcd. for $C_{21}H_{13}F_2N_5O_2$ (M$^+$) requires 405.1037, Found: 405.1037.

Compound 4i-1. A white solid, mp: 322–324 °C. ^{1}H NMR (CD_3COCD_3, 300 MHz, TMS) δ 5.28 (d, 1H, J = 12.3 Hz, CH), 5.53 (d, 1H, J = 6.3 Hz, CH), 6.25 (dd, 1H, J_1 = 12.3 Hz, J_2 = 6.3 Hz, CH), 7.04 (s, 2H, NH_2), 7.33–7.44 (m, 2H, Ar), 7.53–7.82 (m, 6H, Ar); ^{13}C NMR (CD_3COCD_3, 75 MHz, TMS) δ 42.2, 42.4, 43.1, 79.3, 83.8, 111.3, 111.8, 116.9, 126.2, 127.8, 129.2, 131.3, 131.6, 131.8, 132.5, 134.3, 134.8, 135.1, 145.6; IR (CH_2Cl_2): ν 3446, 3358, 3228, 2926, 2208, 1648, 1562, 1473, 1358, 1026, 749 cm^{-1}; MS (EI) m/z (%): 525 [M$^+$] (3.3), 401 (13.4), 399 (13.0), 300 (9.4), 298 (10.2), 220 (16.9), 219 (100), 171 (8.4), 169 (8.3); HRMS (EI) Calcd. for $C_{21}H_{13}Br_2N_5O_2$ (M$^+$) requires 524.9436, Found: 524.9448.

Compound 4j-1. A white solid, mp: 327–329 °C. ^{1}H NMR (CD_3COCD_3, 300 MHz, TMS) δ 5.25 (d, 1H, J = 12.3 Hz, CH), 5.53 (d, 1H, J = 6.3 Hz, CH), 6.26 (dd, 1H, J_1 = 12.3 Hz, J_2 = 6.3 Hz, CH), 7.05 (s, 2H, NH_2), 7.41–7.55 (m, 4H, Ar), 7.51–7.67 (m, 2H, Ar), 7.75–7.83 (m, 2H, Ar); ^{13}C NMR (CD_3COCD_3, 75 MHz, TMS) δ 39.8, 40.6, 42.2, 79.0, 83.7, 111.4, 111.8, 116.9, 128.5, 128.9, 129.8, 130.8, 131.3, 131.6, 132.2, 133.3, 135.7, 136.6, 145.7; IR (CH_2Cl_2): ν 3452, 3357, 3226, 2925, 2209, 1649, 1563, 1477, 1440, 1359, 1040, 752 cm^{-1}; MS (EI) m/z (%): 437 [M$^+$] (6.2), 357 (8.8), 355 (23.5), 256 (7.3), 254 (19.6), 240 (7.1), 220 (20.6), 219 (100), 125 (13.1); HRMS (EI) Calcd. for $C_{21}H_{13}Cl_2N_5O_2$ (M$^+$) requires 437.0446, Found: 437.0447.

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Notes and references

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10 The crystal data of product **4a-1** have been deposited at the CCDC with number 688760.† Empirical formula: $C_{21}H_{16}N_5O_{2.33}$; formula weight: 375.72; crystal size: 0.469 × 0.411 × 0.347; crystal color, habit: colorless, prismatic; crystal system: rhombohedral; lattice type: primitive; lattice parameters: a = 23.2536(10) Å, b = 23.2536(10) Å, c = 17.7700(11) Å, α = 90°, β = 90°, γ = 120°, V = 8321.4(7) Å^3; space group: $R\bar{3}$; Z = 18; D_{calc} = 1.350 g cm^{-3}; F_{000} = 3522; $R1$ = 0.0514, $wR2$ = 0.1330. Diffractometer: Rigaku AFC7R. The crystal data of product **4a-2** have been deposited at the CCDC with number 688759. Empirical formula: $C_{21}H_{15}N_5O_2$; formula weight: 369.38; crystal size: 0.321 × 0.236 × 0.051; crystal color, habit: colorless, prismatic; crystal system: monoclinic; lattice type: primitive; lattice parameters: a = 13.2254(13) Å, b = 11.3377(12) Å, c = 14.1441(15) Å, α = 90°, β = 117.874(2)°, γ = 90°, V = 1874.8(3) Å^3; space group: $P2(1)/c$; Z = 4; D_{calc} = 1.309 g cm^{-3}; F_{000} = 768; $R1$ = 0.0561, $wR2$ = 0.1011. Diffractometer: Rigaku AFC7R.

