Catalyst-Free and Stereoselective Synthesis of N,N-Bicyclic Pyrazolidinone Derivatives

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Received: 11.01.2013; Accepted after revision: 12.03.2013

Abstract: A catalyst-free and stereoselective cycloaddition of pyrazolidin-3-one-derived azomethine imine to *trans*-β-nitrostyrene is described, which allows versatile, efficient and highly enantioselective synthesis of N,N-bicyclic pyrazolidinone derivatives.

Key words: N,N-bicyclic pyrazolidinone, azomethine imine, *trans*-β-nitrostyrene, cycloaddition, stereoselectivity

N,N-Bicyclic pyrazolidinone derivatives are biologically significant compounds and their importance has risen significantly since the late 1980s.[1] They have been developed as analogues of penicillin and cephalosporin antibiotics, herbicides, and pesticides, and as potent drugs for the treatment of cognitive dysfunctions such as Alzheimer's disease (Figure 1). Because of this broad interest, several routes have been developed for the synthesis of N,N-bicyclic pyrazolidinone derivatives. The most common method relies on 1, 3-dipolar cycloaddition of azomethine imines with alkenes or alkynes.[2] A variety of asymmetric cycloadditions of azomethine imines have been reported and most of them have been improved by organic molecular or metal catalysis.[3] To the best of our knowledge, catalyst-free and stereoselective cycloadditions of pyrazolidin-3-one-derived azomethine imines have not been reported. Dorn et al. found that the addition of azomethine imines **A** to *trans*-β-nitrostyrene **B** in refluxing dichloromethane yielded 15–30% of the *cis*-adduct **D** beside the normal *trans*-adduct **C** (Scheme 1).[4] The zwitterion **E** was thought to be responsible for this steric course, but Huisgen et al. could not repeat the results in their following study. In a renewed study of this reaction, we found a highly stereoselective and catalyst-free cycloaddition of pyrazolidin-3-one-derived azomethine imine to *trans*-β-nitrostyrene, which gave different results from those of both Dorn and Huisgen.

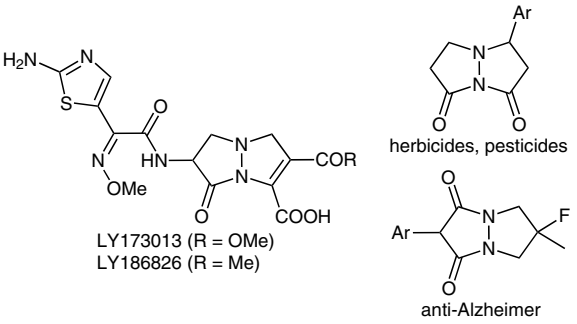
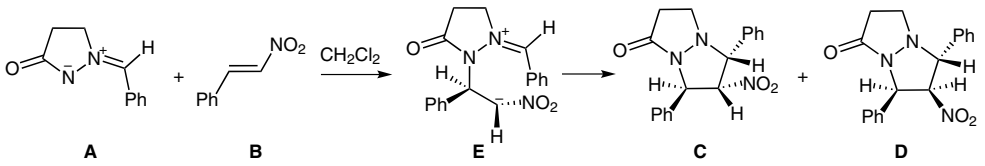


Figure 1 Examples of biologically active N,N-bicyclic pyrazolidinone derivatives

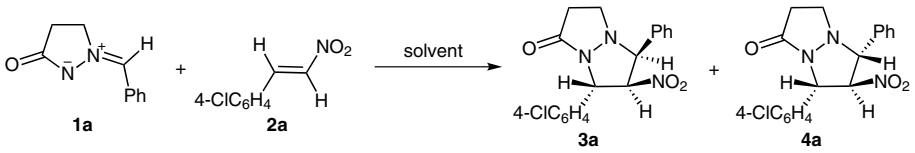
In an initial investigation, we examined the reaction of azomethine imine **1a** with *trans*-β-nitrostyrene **2a** in different solvents. It was found that the reaction in most organic solvents at reflux, such as in chloroform, tetrahydrofuran, acetonitrile and methanol (with comparatively low boiling points), led to cycloaddition product **3a** in good yields in the absence of a catalyst (Table 1, entries 1–5). The stereoselectivity of the product is in accordance with the results of Huisgen. If the reaction was carried out in a polar solvent, such as dimethyl sulfoxide, at 60 °C, a trace amount of **4a** together with the normal product **3a** (entry 6) was formed. Further increasing the reaction temperature resulted in an increased yield of **4a** until almost it was the sole product at temperatures higher than 100 °C (entry 7). This steric course is completely different from both the results of Dorn and Huisgen. The reaction in other polar solvents such as *N*,*N*-dimethylformamide or water led to a mixture of **3a** and **4a** (entries 8 and 9). In order to prove that temperature was not the only factor for this steric course, the same reaction was carried out at the same temperature (about 110 °C) in



Scheme 1 [3+2] Cycloaddition of azomethine imine to *trans*-β-nitrostyrene

SYNTHESIS 2013, 45, 1325–1332
Advanced online publication: 08.04.2013
DOI: 10.1055/s-0032-1316890; Art ID: SS-2013-F0880-OP

Table 1 Reaction of Azomethine Imine **1a** with *trans*-β-Nitrostyrene **2a** in Different Solvents[a]



Entry	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	
				3a	**4a**
1	$CHCl_3$	reflux	8	82	0
2	THF	reflux	8	78	0
3	acetone	reflux	8	80	0
4	MeCN	reflux	8	73	0
5	MeOH	reflux	8	76	0
6	DMSO	60	48	60	trace
7	DMSO	110	48	trace	68
8	DMF	110	48	11	30
9	H_2O	reflux	48	28	10
10	toluene	reflux	48	52	21

[a] All reactions were carried out with **1a** (1.0 mmol), **2a** (1.0 mmol), solvent (5 mL).
[b] Isolated yields.

a nonpolar solvent, toluene. It was found that the yield of **4a** decreased markedly and **3a** was generated as the main product (entry 10). Although the reaction in dimethyl sulfoxide needs a longer reaction time and results in a slightly lower yield, the reaction can result in excellent stereoselectivity in the absence of a catalyst or chiral ligand. So a catalyst-free and stereoselective cycloaddition of pyrazolidin-3-one-derived azomethine imine to *trans*-β-nitrostyrene is achieved solely by changing the reaction medium.

The scope and limitation of this stereoselectivity cycloaddition were explored. The reactions were firstly carried out in refluxing chloroform and products **3** were obtained in good yields as the sole product in all reactions (Table 2). The reaction was found to be tolerant to various substituted azomethine imines and *trans*-β-nitrostyrenes. The substituent on the aromatic ring has no significant effect

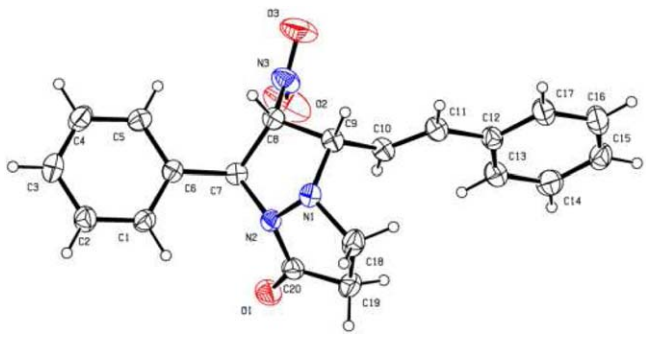
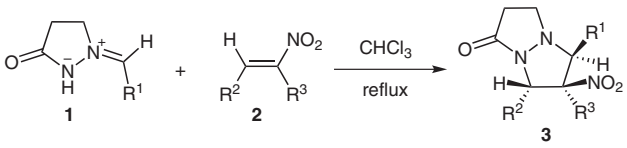


Figure 2 X-ray crystal structure of **3j**

Table 2 Reaction of Azomethine Imine **1** with *trans*-β-Nitrostyrene **2** in Chloroform[a]



Entry	R^1	R^2	R^3	Product	Yield[b] (%)
1	Ph (**1a**)	4-ClC_6H_4	H	**3a**	82
2	Ph (**1a**)	4-BrC_6H_4	H	**3b**	79
3	Ph (**1a**)	Ph	H	**3c**	84
4	Ph (**1a**)	4-MeC_6H_4	H	**3d**	87
5	Ph (**1a**)	2,4-$Cl_2C_6H_3$	H	**3e**	89
6	4-ClC_6H_4 (**1b**)	Ph	H	**3f**	85
7	4-ClC_6H_4 (**1b**)	4-ClC_6H_4	H	**3g**	73
8	4-MeC_6H_4 (**1c**)	4-ClC_6H_4	H	**3h**	72
9	4-$MeOC_6H_4$ (**1d**)	4-ClC_6H_4	H	**3i**	82
10	CH=CHPh (**1e**)	Ph	H	**3j**	88
11	CH=CHPh (**1e**)	2,4-$Cl_2C_6H_3$	H	**3k**	90
12	CH=CHPh (**1e**)	Ph	CH_3	**3l**	70

[a] All reactions were carried out with **1** (1.0 mmol), **2** (1.0 mmol), $CHCl_3$ (5 mL).
[b] Isolated yields.

on this transformation. The structures of the products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic data. In addition, the NMR-based structures were further confirmed by X-ray crystallographic analysis of **3j** (Figure 2).[5]

In contrast, the cycloadditions of pyrazolidin-3-one-derived azomethine imines with *trans*-β-nitrostyrene in dimethyl sulfoxide at 110 °C generated moderate yield of **4** instead of the normal products **3** in most cases (Table 3). The structures of the products were deduced from their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectroscopic data. In addition, the NMR-based structures were further confirmed by the X-ray crystallographic analysis of **4l** (Figure 3).[6] The reactions in dimethyl sulfoxide required a longer time than reactions in chloroform to go to completion. In most cases, they do not go to complete conversion and starting material **2** was recovered. The reaction was found to be tolerant to various substituted azomethine imines and *trans*-β-nitrostyrene (Table 3, entries 1–12).

A possible reaction mechanism via a zwitterion intermediate **5** is proposed as route to product formation (Scheme 2).[7] As shown in Scheme 2, the addition of azomethine imine **1** to *trans*-β-nitrostyrene **2** in a polar aprotic solvent (DMSO) at high temperatures gives compound **4** as the thermodynamically stable product bearing the two substituent groups, NO_2 and R^2 on opposite faces of the five-member ring. For the reaction of azomethine imine **1** to *trans*-β-nitrostyrene **2** in refluxing chloroform, kinetically stable product **3** is generated due to the negative charge attacking the less sterically hindered side of the double bond plane of intermediate **5**. It is presumed that isomerization of cycloadduct **3** to **4**, as the thermodynamically more stable isomer, may occur in polar solvents such as dimethyl sulfoxide at high temperatures through the zwitterion intermediate **5**. So product **3f** (0.5 mmol) in dimethyl sulfoxide (3 mL) was heated at 110 °C for 48 hours. As we expected, product **4f** was isolated in 61% yield after puri-

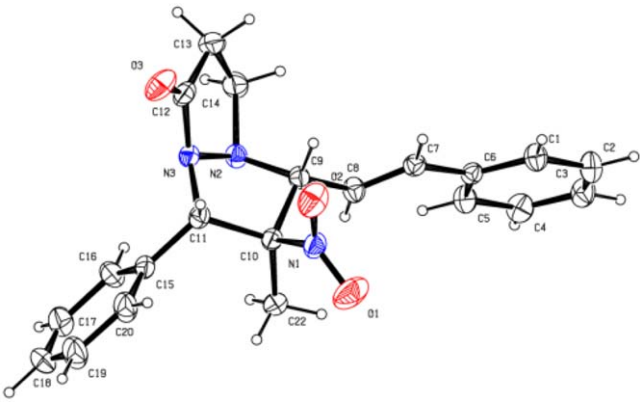
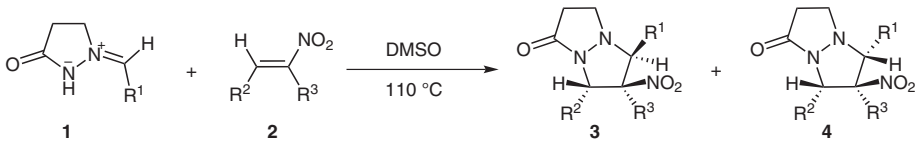


Figure 3 X-ray crystal structure of **4l**

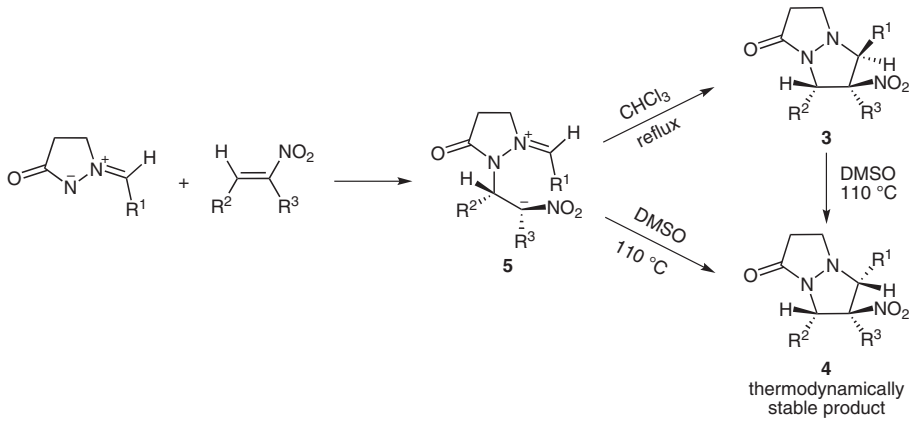
Table 3 Reaction of Azomethine Imine **1** with *trans*-β-Nitrostyrene **2** in Dimethyl Sulfoxide[a]



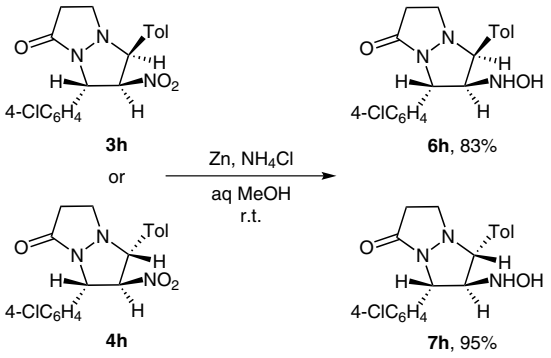
1 **2** **3** **4**

R^1	R^2	R^3	Yield[b] (%) **3**	Yield[b] (%) **4**	Recovery of **2** (%)
Ph (**1a**)	4-ClC_6H_4	H	trace (**3a**)	68 (**4a**)	16 (**2a**)
Ph (**1a**)	4-BrC_6H_4	H	trace (**3b**)	62 (**4b**)	25 (**2b**)
Ph (**1a**)	Ph	H	7 (**3c**)	55 (**4c**)	12 (**2c**)
Ph (**1a**)	4-MeC_6H_4	H	trace (**3d**)	54 (**4d**)	18 (**2d**)
Ph (**1a**)	2,4-$Cl_2C_6H_3$	H	trace (**3e**)	57 (**4e**)	16 (**2e**)
4-ClC_6H_4 (**1b**)	Ph	H	10 (**3f**)	51 (**4f**)	15 (**2c**)
4-ClC_6H_4 (**1b**)	4-ClC_6H_4	H	4 (**3g**)	55 (**4g**)	18 (**2a**)
4-MeC_6H_4 (**1c**)	4-ClC_6H_4	H	trace (**3h**)	52 (**4h**)	20 (**2a**)
4-$MeOC_6H_4$ (**1d**)	4-ClC_6H_4	H	5 (**3i**)	53 (**4i**)	26 (**2a**)
CH=CHPh (**1e**)	Ph	H	trace (**3j**)	56 (**4j**)	19 (**2c**)
CH=CHPh (**1e**)	2,4-$Cl_2C_6H_3$	H	8 (**3k**)	42 (**4k**)	28 (**2e**)
CH=CHPh (**1e**)	Ph	Me	6 (**3l**)	24 (**4l**)	49 (**2f**)

[a] All reactions were carried out with **1** (1.0 mmol), **2** (1.0 mmol), DMSO (5 mL).
[b] Isolated yields.



Scheme 2 Proposed mechanism for the cycloaddition of azomethine imine **1** with *trans*-β-nitrostyrene **2**



Scheme 3 Reduction of **3h** and **4h** to the corresponding hydroxylamines

fication by flashing chromatography. At the same time, *trans*-β-nitrostyrene **2c** was recovered in 15% yield. This result further confirms the rationality of the proposed mechanism and also obviously explains why the starting materials **2** were always recovered in the case of dimethyl sulfoxide.

The utility of this cycloaddition reaction was also proved by the conversion of the nitro group to other functional groups, such as hydroxylamine (Scheme 3). Compounds **3h** and **4h** can be reduced easily to the corresponding hydroxylamines **6h** and **7h** using zinc/ammonium chloride in aqueous methanol in high yields, 83% and 95%, respectively.[8]

In conclusion, we present herein an interesting example of catalyst-free and stereoselective synthesis of N,N-bicyclic pyrazolidinone derivatives. From a synthetic point of view, this is of interest because of the possibility of selectively synthesizing biologically significant N,N-bicyclic pyrazolidinone derivatives by simply changing the reaction medium. Further studies on the reaction mechanism of this ring-closing reaction and its application the preparation of other N,N-bicyclic pyrazolidinone derivatives as well as to the synthesis of natural products are currently underway.

All reagents were used directly as obtained commercially unless otherwise noted. Melting points were determined on a microscopic apparatus and are uncorrected. Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded at 300 MHz and 400 MHz in $CDCl_3$ (δ = 7.24 ppm) and ^{13}C NMR spectra were recorded at 75 MHz and 100 MHz in $CDCl_3$ (δ = 77.00 ppm) using TMS as internal standard. Nicolet iS10 FT-IR spectrophotometer was used for IR spectra. HRMS spectra were obtained with a micrOTOF-Q II instrument. The starting azomethine imines **1a–e** were synthesized according to the literature.[3g]

(5*S,6*R**,7*S**)-6-Nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazolones 3; General Procedure**

A mixture of azomethine imine **1** (1.0 mmol), *trans*-β-nitrostyrene **2** (1.0 mmol) in $CHCl_3$ (5 mL) was heated to reflux until TLC showed complete consumption of *trans*-β-nitrostyrene **2** (ca. 8–12 h); the mixture was cooled to r.t. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel) to give products **3**.

(5*R,6*R**,7*S**)-6-Nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazolones 4; General Procedure**

A mixture of azomethine imines **1** (1.0 mmol), *trans*-β-nitrostyrene **2** (1.0 mmol) in DMSO (5 mL) was heated at 110 °C for ca. 48 h. The mixture was cooled to r.t. and H_2O (15 mL) was added and the mixture was extracted with EtOAc (3 × 30 mL). The combined extracts were washed with H_2O and brine, and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel) to give products **4**.

Isomerization of Cycloadduct 3f to 4f

A mixture of cycloadduct **3f** (0.5 mmol) in DMSO (3 mL) was heated at 110 °C for ca. 48 h. The mixture was then cooled to r.t. and H_2O (10 mL) was added and the mixture was extracted with EtOAc (3 × 20 mL). The combined extracts were washed with H_2O and brine, and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel) to give **4f**.

Reduction of Compounds 3h and 4h to the Corresponding Hydroxylamines 6h and 7h; General Procedure

To a stirred soln of the nitro compound **3h** or **4h** (1.0 mmol) in MeOH–sat. NH_4Cl (4:1, 8 mL) was added Zn dust (10 mmol) portionwise over 15 min at r.t. The mixture was stirred for several hours at r.t. After completion of the reaction (TLC), EtOAc (20 mL) was added and the mixture was filtered. The filtrate was washed with H_2O and brine, and then dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography (silica gel) to give hydroxylamines **6h** and **7h**.

(5*S,6*R**,7*S**)-7-(4-Chlorophenyl)-6-nitro-5-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3a)**
Yellow solid; yield: 0.293 g (82%); mp 181–182 °C.

IR (KBr): 3009, 1678, 1552, 1494, 1378, 830, 759, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.31 (m, 9 H), 5.66 (d, *J* = 2.1 Hz, 1 H), 5.27 (dd, *J* = 2.4, 4.8 Hz, 1 H), 4.33 (d, *J* = 4.8 Hz, 1 H), 3.53–3.48 (m, 1 H), 3.03–2.95 (m, 1 H), 2.85–2.83 (m, 1 H), 2.72–2.66 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 135.1, 133.7, 130.3, 129.9, 129.6, 129.3, 128.0, 127.7, 99.3, 70.7, 59.0, 49.4, 35.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{16}ClN_3NaO_3$: 380.0772; found: 380.0773.

(5*R,6*R**,7*S**)-7-(4-Chlorophenyl)-6-nitro-5-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4a)**
White solid; yield: 0.242 g (68%); mp 154–156 °C.

IR (KBr): 2957, 1716, 1569, 1496, 1365, 838, 745, 704 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.24 (m, 9 H), 5.64 (d, *J* = 3.3 Hz, 1 H), 5.03 (dd, *J* = 3.3, 6.0 Hz, 1 H), 4.26 (d, *J* = 6.0 Hz, 1 H), 3.67–3.59 (m, 1 H), 3.20–3.13 (m, 1 H), 2.97–2.88 (m, 1 H), 2.75–2.67 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2, 136.6, 134.4, 133.7, 129.6, 129.3, 129.2, 127.8, 127.5, 100.2, 73.7, 61.4, 44.5, 28.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{16}ClN_3NaO_3$: 380.0772; found: 380.0772.

(5*S,6*R**,7*S**)-7-(4-Bromophenyl)-6-nitro-5-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3b)**
Yellow solid; yield: 0.316 g (79%); mp 192–193 °C.

IR (KBr): 3007, 1677, 1551, 1490, 1376, 825, 756, 699 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.59–7.26 (m, 9 H), 5.64 (d, *J* = 2.1 Hz, 1 H), 5.26 (dd, *J* = 2.4, 4.8 Hz, 1 H), 4.33 (d, *J* = 4.8 Hz, 1 H), 3.52–3.48 (m, 1 H), 3.02–2.82 (m, 2 H), 2.72–2.66 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 134.3, 132.5, 130.3, 129.9, 129.3, 128.3, 127.7, 123.3, 99.1, 70.7, 59.0, 49.3, 35.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{16}BrN_3NaO_3$: 424.0267; found: 424.0278.

(5*R,6*R**,7*S**)-7-(4-Bromophenyl)-6-nitro-5-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4b)**
White solid; yield: 0.248 g (62%); mp 174–175 °C.

IR (KBr): 2954, 1716, 1569, 1492, 1366, 830, 744, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.55–7.31 (m, 9 H), 5.62 (d, *J* = 3.6 Hz, 1 H), 5.03 (dd, *J* = 3.6, 6.0 Hz, 1 H), 4.25 (d, *J* = 6.0 Hz, 1 H), 3.67–3.59 (m, 1 H), 3.20–3.13 (m, 1 H), 2.97–2.90 (m, 1 H), 2.75–2.68 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 137.2, 133.7, 132.3, 129.6, 129.3, 127.8, 122.6, 100.1, 73.8, 61.5, 44.6, 28.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{16}BrN_3NaO_3$: 424.0267; found: 424.0284.

(5*S,6*R**,7*S**)-6-Nitro-5,7-diphenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3c)**
Yellow solid; yield: 0.271 g (84%); mp 149–151 °C.

IR (KBr): 3006, 1691, 1553, 1496, 1371, 752, 700 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.30 (m, 10 H), 5.63 (d, *J* = 1.8 Hz, 1 H), 5.26 (dd, *J* = 1.8, 4.8 Hz, 1 H), 4.32 (d, *J* = 4.8 Hz, 1 H), 3.52–3.47 (m, 1 H), 2.99–2.87 (m, 2 H), 2.71–2.65 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 135.0, 130.4, 129.7, 129.3, 129.1, 129.0, 127.6, 126.5, 99.6, 70.4, 59.6, 49.7, 36.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{17}N_3NaO_3$: 346.1162; found: 346.1147.

(5*R,6*R**,7*S**)-6-Nitro-5,7-diphenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4c)**
Pale yellow solid; yield: 0.178 g (55%); mp 128–129 °C.

IR (KBr): 2925, 1712, 1556, 1496, 1367, 732, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.31 (m, 10 H), 5.68 (d, *J* = 3.6 Hz, 1 H), 5.01 (dd, *J* = 3.6, 6.0 Hz, 1 H), 4.26 (d, *J* = 6.0 Hz, 1 H), 3.68–3.60 (m, 1 H), 3.19–3.13 (m, 1 H), 2.98–2.89 (m, 1 H), 2.77–2.69 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.8, 138.1, 133.9, 129.6, 129.2, 128.5 127.8, 126.0, 100.4, 74.0, 62.0, 44.7, 29.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{17}N_3NaO_3$: 346.1162; found: 346.1170.

(5*S,6*R**,7*S**)-6-Nitro-5-phenyl-7-(4-tolyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3d)**
Yellow solid; yield: 0.293 g (87%); mp 182–183 °C.

IR (KBr): 3009, 1681, 1550, 1516, 1375, 818, 750, 701 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.23 (m, 9 H), 5.60 (d, *J* = 2.1 Hz, 1 H), 5.25 (dd, *J* = 2.4, 6.3 Hz, 1 H), 4.31 (d, *J* = 6.3 Hz, 1 H), 3.54–3.50 (m, 1 H), 3.00–2.89 (m, 2 H), 2.77–2.70 (m, 1 H), 2.37 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 139.1, 131.9, 130.5, 130.0, 129.7, 129.1, 127.5, 126.5, 99.9, 70.6, 59.6, 50.1, 36.3, 21.2.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{20}N_3O_3$: 338.1499; found: 338.1513.

(5*R,6*R**,7*S**)-6-Nitro-5-phenyl-7-(4-tolyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4d)**
Yellow solid; yield: 0.182 g (54%); mp 129–130 °C.

IR (KBr): 2924, 1717, 1569, 1519, 1365, 826, 741, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 9 H), 5.65 (d, *J* = 3.0 Hz, 1 H), 5.09 (dd, *J* = 3.6, 6.0 Hz, 1 H), 4.25 (d, *J* = 6.0 Hz, 1 H), 3.66–3.57 (m, 1 H), 3.18–3.11 (m, 1 H), 2.96–2.87 (m, 1 H), 2.75–2.67 (m, 1 H), 1.66 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.5, 138.3, 135.2, 134.0, 129.8, 129.5, 129.2, 127.8, 126.0, 100.5, 74.0, 61.9, 44.8, 29.2, 21.1.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{19}N_3NaO_3$: 360.1319; found: 360.1314.

(5*S,6*R**,7*S**)-7-(2,4-Dichlorophenyl)-6-nitro-5-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3e)**
White solid; yield: 0.348 g (89%); mp 190–192 °C.

IR (KBr): 2997, 1680, 1554, 1473, 1372, 825, 747, 703 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.47–7.29 (m, 8 H), 5.90 (s, 1 H), 5.15 (dd, *J* = 1.2, 4.8 Hz, 1 H), 4.09 (d, *J* = 4.5 Hz, 1 H), 3.58–3.54 (m, 1 H), 3.18–3.09 (m, 1 H), 2.90–2.77 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 135.6, 133.4, 130.3, 129.9, 129.2, 128.8, 127.7, 127.3, 98.9, 70.1, 56.9, 50.8, 36.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{15}Cl_2N_3NaO_3$: 414.0383; found: 414.0383.

(5*R,6*R**,7*S**)-7-(2,4-Dichlorophenyl)-6-nitro-5-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4e)**
White solid; yield: 0.222 g (57%); mp 180–181 °C.

IR (KBr): 2941, 1725, 1556, 1471, 1363, 820, 742, 705 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.58–7.21 (m, 8 H), 6.08 (d, *J* = 2.7 Hz, 1 H), 4.92 (dd, *J* = 2.4, 5.4 Hz, 1 H), 4.08 (d, *J* = 5.7Hz, 1 H), 3.73–3.65 (m, 1 H), 3.23–3.17 (m, 1 H), 3.02–2.93 (m, 1 H), 2.77–2.69 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5, 135.0, 134.0, 133.1, 129.7, 129.6, 129.3, 128.6, 127.7, 100.5, 75.7, 59.7, 44.6, 28.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{15}Cl_2N_3NaO_3$: 414.0383; found: 414.0377.

(5*S,6*R**,7*S**)-5-(4-Chlorophenyl)-6-nitro-7-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3f)**
White solid; yield: 0.303 g (85%); mp 177–178 °C.

IR (KBr): 2837, 1686, 1553, 1492, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.26 (m, 9 H), 5.62 (s, 1 H), 5.25 (dd, *J* = 2.0, 6.0 Hz, 1 H), 4.28 (d, *J* = 6.0 Hz, 1 H), 3.54–3.48 (m, 1 H), 3.02–2.90 (m, 2 H), 2.77–2.69 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.6, 135.9, 134.8, 129.5, 129.3, 129.1, 126.6, 99.7, 69.9, 59.8, 50.0, 36.3.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{16}ClN_3NaO_3$: 380.0772; found: 380.0777.

(5*R,6*R**,7*S**)-5-(4-Chlorophenyl)-6-nitro-7-phenyltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4f)**
Sticky oil; yield: 0.182 g (51%).

IR (KBr): 2925, 2854, 1719, 1554, 1492, 697 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.24 (m, 9 H), 5.68 (d, *J* = 3.6 Hz, 1 H), 5.04 (dd, *J* = 3.6, 5.7 Hz, 1 H), 4.23 (d, *J* = 5.7 Hz, 1 H), 3.68–3.60 (m, 1 H), 3.16–3.10 (m, 1 H), 2.97–2.87 (m, 1 H), 2.77–2.69 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 137.9, 135.6, 132.6, 129.5, 129.2, 128.6, 126.0, 100.3, 73.2, 61.9, 44.7, 29.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{16}ClN_3NaO_3$: 380.0772; found: 380.0761.

(5*S,6*R**,7*S**)-5,7-Bis(4-chlorophenyl)-6-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3g)**
Yellow solid; yield: 0.285 g (73%); mp 186–188 °C.

IR (KBr): 3007, 1686, 1549, 1493, 1367, 825, 774 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 8 H), 5.59 (d, *J* = 2.1 Hz, 1 H), 5.21 (dd, *J* = 2.1, 4.8 Hz, 1 H), 4.25 (d, *J* = 4.8 Hz, 1 H), 3.49–3.45 (m, 1 H), 2.96–2.84 (m, 2 H), 2.74–2.66 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 136.0, 135.2, 133.3, 129.6, 129.5, 129.4, 129.0, 128.8, 128.0, 99.3, 70.0, 59.0, 49.6, 36.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{15}Cl_2N_3NaO_3$: 414.0383; found: 414.0393.

(5*R,6*R**,7*S**)-5,7-Bis(4-chlorophenyl)-6-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4g)**
Pale yellow solid; yield: 0.215 g (55%); mp 182–183 °C.

IR (KBr): 2979, 1708, 1556, 1492, 1371, 829, 750 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.26 (m, 8 H), 5.64 (d, *J* = 3.6 Hz, 1 H), 4.97 (dd, *J* = 3.6, 6.0 Hz, 1 H), 4.24 (d, *J* = 6.0 Hz, 1 H), 3.67–3.60 (m, 1 H), 3.14–3.10 (m, 1 H), 2.95–2.86 (m, 1 H), 2.75–2.68 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.0, 138.5, 135.7, 134.6, 132.4, 129.5, 129.4, 129.2, 127.5, 100.0, 73.0, 61.3, 44.6, 28.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{15}Cl_2N_3NaO_3$: 414.0383; found: 414.0379.

(5*S,6*R**,7*S**)-7-(4-Chlorophenyl)-6-nitro-5-(4-tolyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3h)**
Pale yellow solid; yield: 0.267 g (72%); mp 183–184 °C.

IR (KBr): 3007, 1692, 1547, 1492, 1367, 825 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.15 (m, 8 H), 5.63 (d, *J* = 2.1 Hz, 1 H), 5.22 (dd, *J* = 2.1, 4.8 Hz, 1 H), 4.29 (d, *J* = 4.8 Hz, 1 H), 3.46–3.42 (m, 1 H), 3.00–2.92 (m, 1 H), 2.76–2.61 (m, 2 H), 2.33 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.7, 139.9, 135.0, 133.8, 130.0, 129.5, 128.0, 127.6, 127.1, 99.1, 70.5, 58.9, 49.1, 35.7, 21.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{18}ClN_3NaO_3$: 394.0929; found: 394.0941.

(5*R,6*R**,7*S**)-7-(4-Chlorophenyl)-6-nitro-5-(4-tolyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4h)**
White solid; yield: 0.193 g (52%); mp 172–173 °C.

IR (KBr): 2983, 1708, 1554, 1492, 1371, 827 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.17 (m, 8 H), 5.65 (d, *J* = 3.6 Hz, 1 H), 5.03 (dd, *J* = 3.6, 6.3 Hz, 1 H), 4.22 (d, *J* = 6.0 Hz, 1 H), 3.67–3.59 (m, 1 H), 3.21–3.14 (m, 1 H), 2.98–2.89 (m, 1 H), 2.77–2.69 (m, 1 H), 2.35 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 139.7, 136.7, 134.4, 130.4, 129.9 129.3, 127.7, 127.5, 100.2, 73.8, 61.4, 44.5, 28.9, 21.2.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{18}ClN_3NaO_3$: 394.0929; found: 394.0929.

(5*S,6*R**,7*S**)-7-(4-Chlorophenyl)-5-(4-methoxyphenyl)-6-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3i)**
Yellow solid; yield: 0.317 g (82%); mp 182–184 °C.

IR (KBr): 3005, 1676, 1548, 1515, 1366, 828 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.34–6.86 (m, 8 H), 5.64 (d, *J* = 2.1 Hz, 1 H), 5.21 (dd, *J* = 2.4, 5.1 Hz, 1 H), 4.29 (d, *J* = 5.1 Hz, 1 H), 3.78 (s, 3 H), 3.44–3.39 (m, 1 H), 2.98–2.93 (m, 1 H), 2.74–2.60 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.9, 160.7, 135.0, 130.4, 129.5, 129.0, 128.0, 121.9 114.7, 99.0, 70.3, 58.8, 55.3, 48.9, 35.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{18}ClN_3O_4$: 410.0878; found: 410.0888.

(5*R,6*R**,7*S**)-7-(4-Chlorophenyl)-5-(4-methoxyphenyl)-6-nitrotetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4i)**
Pale yellow solid; yield: 0.205 g (53%); mp 137–139 °C.

IR (KBr): 2977, 1709, 1555, 1516, 1374, 830 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–6.86 (m, 8 H), 5.62 (d, *J* = 3.6 Hz, 1 H), 4.99 (dd, *J* = 3.6, 6.0 Hz, 1 H), 4.18 (d, *J* = 6.0 Hz, 1 H), 3.78 (s, 3 H), 3.64–3.56 (m, 1 H), 3.18–3.11 (m, 1 H), 2.96–2.86 (m, 1 H), 2.74–2.66 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.1, 160.5, 136.7, 134.4, 129.3, 129.1, 127.5, 125.3, 114.6, 100.2, 73.6, 61.3, 55.3, 44.4, 28.9.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{19}H_{18}ClN_3O_4$: 410.0878; found: 410.0888.

(5*S,6*R**,7*S**)-6-Nitro-7-phenyl-5-styryltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3j)**
Yellow solid; yield: 0.307 g (88%); mp 129–131 °C.

IR (KBr): 3061, 3030, 2985, 1700, 1556, 1495, 1361, 976, 754, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.28 (m, 10 H), 6.78 (d, *J* = 11.7 Hz, 1 H), 5.90 (dd, *J* = 6.9, 11.7 Hz, 1 H), 5.75 (d, *J* = 3.9 Hz, 1 H), 5.32 (dd, *J* = 3.9, 4.8 Hz, 1 H), 4.19–4.15 (m, 1 H), 3.51–3.36 (m, 2 H), 2.76–2.69 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 139.8, 136.6, 134.9, 129.1, 128.8, 126.9, 126.2, 96.5, 69.2, 58.8, 45.7, 33.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}N_3NaO_3$: 372.1319; found: 372.1315.

(5*R,6*R**,7*S**)-6-Nitro-7-phenyl-5-styryltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4j)**
Yellow solid; yield: 0.195 g (56%); mp 137–139 °C.

IR (KBr): 3063, 3029, 2964, 1709, 1557, 1496, 1364, 976, 751, 689 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.28 (m, 10 H), 6.75 (d, *J* = 12.0 Hz, 1 H), 6.10 (dd, *J* = 6.3, 12.0 Hz, 1 H), 5.68 (d, *J* = 3.6 Hz, 1 H), 5.07 (dd, *J* = 3.6, 6.0 Hz, 1 H), 3.87–3.83 (m, 1 H), 3.68–3.62 (m, 1 H), 3.34–3.30 (m, 1 H), 2.92–2.85 (m, 1 H), 2.74–2.71 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 175.7, 138.0, 137.8, 135.0, 130.9, 129.1, 128.9, 127.7, 128.5, 126.8, 125.9, 121.8, 98.2, 73.4, 61.6, 44.4, 29.0.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{19}N_3NaO_3$: 372.1319; found: 372.1329.

(5*S,6*R**,7*S**)-7-(2,4-Dichlorophenyl)-6-nitro-5-styryltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3k)**
White solid; yield: 0.375 g (90%); mp 158–159 °C.

IR (KBr): 3061, 3027, 2996, 1683, 1553, 1496, 1373, 974, 826, 745, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.28 (m, 8 H), 6.75 (d, *J* = 11.7 Hz, 1 H), 6.02 (d, *J* = 2.4 Hz, 1 H), 5.88 (dd, *J* = 3.6, 11.7 Hz, 1 H), 5.19 (dd, *J* = 2.1, 4.8 Hz, 1 H), 4.05–4.01 (m, 1 H), 3.57–3.53 (m, 1 H), 3.30–3.23 (m, 1 H), 2.91–2.72 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.9, 139.4, 135.4, 134.9, 133.2, 132.0, 130.0, 129.2, 128.8, 128.7, 127.7, 127.0, 116.4, 96.3, 68.7, 57.0, 52.0, 47.1, 34.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{17}Cl_2N_3NaO_3$: 440.0539; found: 440.0525.

(5*R,6*R**,7*S**)-7-(2,4-Dichlorophenyl)-6-nitro-5-styryltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4k)**
Pale yellow solid; yield: 0.175 g (42%); mp 148–149 °C.

IR (KBr): 3059, 3025, 2992, 1702, 1553, 1494, 1370, 969, 827, 751, 690 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.26 (m, 8 H), 6.65 (d, *J* = 12.0 Hz, 1 H), 6.06–6.00 (m, 2 H), 4.88 (dd, *J* = 3.0, 5.7 Hz, 1 H), 3.75–3.66 (m, 2 H), 3.38–3.32 (m, 1 H), 2.98–2.88 (m, 1 H), 2.76–2.68 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.3, 138.0, 135.0, 134.8, 134.0, 133.0, 129.6, 129.0, 128.7, 128.6, 127.6, 126.8, 121.7, 98.3, 75.0, 59.4, 44.2, 28.5.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{20}H_{17}Cl_2N_3NaO_3$: 440.0539; found: 440.0541.

(5*S,6*R**,7*S**)-6-Methyl-6-nitro-7-phenyl-5-styryltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (3l)**
Yellow solid; yield: 0.254 g (70%); mp 149–151 °C.

IR (KBr): 3069, 2980, 2917, 1676, 1538, 1499, 1341, 973, 774, 754, 703 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45–7.26 (m, 10 H), 6.73 (d, *J* = 15.9 Hz, 1 H), 5.93–5.85 (m, 2 H), 3.62–3.50 (m, 2 H), 3.22–3.12 (m, 1 H), 2.99–2.90 (m, 1 H), 2.87–2.70 (m, 1 H), 1.29 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 139.0, 135.1, 133.9, 129.0, 128.8, 127.3, 126.9, 117.8, 101.6, 75.1, 62.2, 48.7, 35.2, 20.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{21}N_3NaO_3$: 386.1475; found: 386.1473.

(5*R,6*R**,7*S**)-6-Methyl-6-nitro-7-phenyl-5-styryltetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (4l)**
Pale yellow solid; yield: 0.087 g (24%); mp 125–126 °C.

IR (KBr): 3032, 3007, 2924, 1716, 1537, 1495, 1346, 976, 765, 753, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.27 (m, 10 H), 6.76 (d, *J* = 12.0 Hz, 1 H), 6.00 (dd, *J* = 6.0, 12.0 Hz, 1 H), 5.77 (s, 1 H), 4.02 (d, *J* = 6.0 Hz, 1 H), 3.74–3.66 (m, 1 H), 3.34–3.27 (m, 1 H), 2.89–2.80 (m, 1 H), 2.78–2.71 (m, 1 H), 1.22 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.4, 138.1, 135.4, 135.2, 128.8, 128.6, 128.5, 127.4, 126.8, 120.1, 99.8, 75.1, 65.0, 45.1, 29.5, 19.6.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{21}N_3NaO_3$: 386.1475; found: 386.1479.

(5*S,6*R**,7*S**)-7-(4-Chlorophenyl)-6-(hydroxyamino)-5-(4-tolyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (6h)**
White solid; yield: 0.297 g (83%); mp 204–205 °C.

IR (KBr): 3400, 3280, 1670, 1490, 1371, 1010, 818 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.31 (m, 4 H), 7.20 (s, 4 H), 5.52 (s, 1 H), 5.12 (br, 1 H), 5.07 (s, 1 H), 3.94 (d, *J* = 5.6 Hz, 1 H), 3.76 (d, *J* = 4.4 Hz, 1 H), 3.59–3.55 (m, 1 H), 3.05–2.96 (m, 1 H), 2.90–2.83 (m, 1 H), 2.75–2.69 (m, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.1, 138.6, 135.7, 133.7, 129.8, 129.1, 129.0, 127.9, 127.6, 78.1, 69.1, 59.9, 51.2, 36.5, 21.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{22}ClN_3O_2$: 358.1317; found: 358.1308.

(5*R,6*R**,7*S**)-7-(4-Chlorophenyl)-6-(hydroxyamino)-5-(4-tolyl)tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazol-1-one (7h)**
White solid; yield: 0.340 g (95%); mp 174–176 °C.

IR (KBr): 3340, 3280, 1670, 1490, 1371, 1010, 803 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.4 Hz, 2 H), 7.27–7.21 (m, 4 H), 7.14 (d, *J* = 8.0 Hz, 2 H), 6.53 (s, 1 H), 5.33 (s, 1 H), 5.25 (d, *J* = 5.2 Hz, 1 H), 3.79 (d, *J* = 8.4 Hz, 1 H), 3.61–3.53 (m, 2 H), 3.07–3.00 (m, 1 H), 2.89–2.71 (m, 1 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.5, 139.0, 138.4, 133.3, 133.1, 129.6 128.7, 127.7, 127.5, 81.8, 70.4, 59.1, 46.6, 31.1, 21.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{22}ClN_3O_2$: 358.1317; found: 358.01.

Acknowledgment

The authors gratefully acknowledge the support of this work supported by Shaanxi Provincial Natural Science Foundation of China (No.2009K01-51).

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

References

(1) (a) Jungheim, L. N.; Sigmund, S. K. *J. Org. Chem.* **1987**, *52*, 4007. (b) Ternansky, R. J.; Draheim, S. E.; Pike, A. J.; Counter, F. T.; Eudaly, J. A.; Kasher, J. S. *J. Med. Chem.* **1993**, *36*, 3224. (c) Fischer, R.; Bretschneider, T.; Gesing, E. R. F.; Feucht, D.; Kuck, K.-H.; Loesel, P.; Malsam, O.; Arnold, C.; Auler, T.; Hills, M. J.; Kehne, H. WO 2005016873, **2005**; *Chem. Abstr.* **2005**, *142*, 261530. (d) Kosower, E. M.; Hershkowitz, E. IL 94658, **1994**; *Chem. Abstr.* **1994**, *122*, 214077.

(2) (a) Chuang, T.-H.; Sharpless, K. B. *Helv. Chim. Acta* **2000**, *83*, 1734. (b) Panfil, I.; Urbańczyk-Lipkowska, Z.; Sunwińska, K.; Solecka, J.; Chmielewski, M. *Tetrahedron* **2002**, *58*, 1199. (c) Pezdirc, L.; Jovanovski, V.; Bevk, D.; Jakše, R.; Pirc, S.; Meden, A.; Stanovnik, B.; Svete, J. *Tetrahedron* **2005**, *61*, 3977. (d) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818.

(3) (a) Shintani, R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 10778. (b) Surez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (c) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2007**, *46*, 7667. (d) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (e) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971. (f) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (g) Keller, M.; Sani Souna Sido, A.; Pale, P.; Sommer, J. *Chem. Eur. J.* **2009**, *15*, 2810. (h) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu,

H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076. (i) Suga, H.; Arikawa, T.; Itoh, K.; Okumura, Y.; Kakehi, A.; Shiro, M. *Heterocycles* **2010**, *81*, 1669.

(4) Huisgen, R.; Weinberger, R. *Tetrahedron Lett.* **1985**, *26*, 5119.

(5) Crystallographic data (excluding structure factors) for the structures in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no: CCDC 889429 (**3j**): $C_{20}H_{19}N_3O_3$, MW = 349.38, T = 296(2) K, λ = 0.71073 Å, triclinic, space group $P\bar{1}$, a = 10.110(6) Å, b = 10.543(6) Å, c = 10.574(6) Å, α = 111.884(4), β = 116.290(4), γ = 98.533(5), V = 868.6(8) Å^3, Z = 2, Dc = 1.336 mg/m^3, μ = 0.092 mm^{-1}, F(000) = 368. Crystal size 0.23 × 0.22 × 0.19 mm^3; independent reflections: 6525 [R(int) = 0.0303]; reflections collected: 3349: refinement method: full-matrix least-squares on $F$2; goodness-of-fit on $F$2: 1.037; final R indices [$I > 2\sigma$ (I)] $R$1 = 0.0530, wR2 = 0.1278; R indices (all data): $R$1 = 0.0788, wR2 = 0.1438; extinction coefficient: 0.055(5); largest diff. peak and hole: 0.549 and –0.402 e Å^{-3}. Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (internat.) +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk.

(6) Crystal data for **4l** have deposited in CCDC as deposition number 889430: $C_{21}H_{21}N_3O_3$, MW = 363.41, T = 296(2) K, λ = 0.71073 Å, monoclinic, space group $P$2(1)/c, a = 13.616(12) Å, b = 12.482(12) Å, c = 12.482(12) Å, α = 90.00, β = 114.332(9), γ = 90.00, V = 1933 (3) Å^3, Z = 4, Dc = 1.249 mg/m^3, μ = 0.085 mm^{-1}, F(000)=768. Crystal size 0.23 × 0.21 × 0.16 mm; independent reflections: 10992 [R(int) = 0.0411]; reflections collected: 3595; refinement method: full-matrix least-squares on $F$2; goodness-of-fit on $F$2: 1.009; final R indices [$I > 2\sigma$ (I)] $R$1 = 0.0544, wR2 = 0.1295; R indices (all data): $R$1 = 0.1091, wR2 = 0.1642; largest diff. peak and hole: 0.282 and –0.207 e Å^{-3}.

(7) (a) Zhang, Y.; Raines, A. J.; Flowers, R. A. II *Org. Lett.* **2003**, *5*, 2363. (b) Acevedo, O.; Squillacote, M. E. *J. Org. Chem.* **2008**, *73*, 912.

(8) (a) Saikia, P. P.; Baishya, G.; Goswami, A.; Barua, N. C. *Tetrahedron Lett.* **2008**, *49*, 6508. (b) Rahaim, R. J. Jr.; Maleczka, R. E. Jr. *Org. Lett.* **2005**, *7*, 5087.

