Tetrahedron 67 (2011) 3209–3215

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Regioselective 1,3-dipolar cycloaddition of nitrilimines to 2-methyl-2-vinyl oxirane

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ARTICLE INFO

Article history:
Received 26 November 2010
Received in revised form 16 February 2011
Accepted 7 March 2011
Available online 12 March 2011

Keywords:
Nitrilimine
Vinyl oxirane
Regioselective
Pyrazole

ABSTRACT

1,3-Dipolar cycloaddition of in situ generated *C*,*N*-diaryl nitrilimines to 2-methyl-2-vinyl oxirane gives rise to the regioselective formation of novel 5-(2-methyloxiranyl)-4,5-dihydropyrazole derivatives in moderate to good yields. The structures and stereochemistries of the new cycloadducts were confirmed by spectroscopic/physical methods including X-ray diffraction data.

1. Introduction

1,3-Dipolar cycloaddition reactions occupy a significant place due to their versatility in the construction of five-membered heterocylic systems.[1] Most especially, nitrilimines have been utilized in many cycloaddition reactions (generated in situ) and thus, pyrazole- and pyrazoline-containing heterocycles have been intensively synthesized for many years by using ethylenic, heterocyclic dipolarophiles[2–9] in the presence of different catalysts.[10,11]

In general, 1,3-dipolar cycloaddition reactions of nitrilimines with a dipolarophile having nonidentical terminal π-centers, such as monosubstituted ethylenes can lead theoretically to the 5- and 4-substituted 2-pyrazolines (regioisomers). Many examples reported in the literature showed that the orientation observed for alkenes substituted with electron-donor, conjugating, and moderate electron-acceptor substituents is the 5-substituted regioisomer.[12,13] The rationalization of such regiochemical results became evident in terms of the frontier molecular orbital theory of Fukui.[14–16]

In addition, vinyl oxiranes are simple 2-alkenyl substituted epoxides, which are attractive precursors for the construction of functionalized four- and five-membered or larger rings by Pd-catalyzed or intramolecular Friedel–Craft reactions.[17–19]

The only reported cycloaddition reaction of vinyl oxiranes involved heterocumulenes; isocyanates and carbodiimides were used as reagents.[20]

In this regard, to the best of our knowledge, since there is no example of nitrilimine cycloaddition reactions to vinyl oxirane derivatives, we have been interested in the present work to study 1,3-dipolar cycloaddition of diaryl substituted nitrilimines to 2-methyl-2-vinyl oxirane.

2. Results and discussion

We performed the cycloaddition reaction of nitrilimines obtained initially in situ from the treatment of *C*,*N*-diaryl substituted α-chloro hydrazones with the excess triethylamine in dry dichloromethane then with the addition of excess 2-methyl-2-vinyl oxirane at room temperature. The progress of the reaction was followed by TLC until all diarylnitrilimine has been consumed. The overall reaction yielded a mixture of diastereomers (*RR*,*RS*) in moderate to good yields (40–92%) with low diastereoselectivity (Scheme 2). 5*R*,2′*R*-**6** and 5*R*,2′*S*-**7** diastereomers have been obtained in the ratios between 62:38 and 36:64 (Table 1 and Scheme 1).

Table 1
Diastereomeric ratios and yields of title compounds **6**–**7**(**a**–**h**)

Compd	R^1	R^2	Reaction time (h)	Et_3N (equiv)	2M2VO (equiv)	Yield (%)[a]	Diastereomeric ratio (5*R*,2*R*-6:5*R*,2*S*-7)
6a–**7a**	H	H	24	10	3	92	54:46 (i)[b]
6b–**7b**	CH_3	H	64	8	3	80	62:38 (i)[b]
6c–**7c**	NO_2	H	48	8	2	40	50:50 (s)
6d–**7d**	OCH_3	H	20	10	3	65	57:43 (i)[b]
6e–**7e**	CF_3	H	96	8	3	84	53:47 (s)
6f–**7f**	Br	Cl	44	8	3	95	58:42 (i)[b]
6g–**7g**	NO_2	Cl	64	9	3	64	36:64 (s)
6h–**7h**	CH_3	CN	96	8	3	84	56:44 (i)[b]

[a] Total yields of diastereomeric cycloadducts.
[b] Assigned isomeric ratio using ^{1}H NMR. i=inseparable mixture s=separated.

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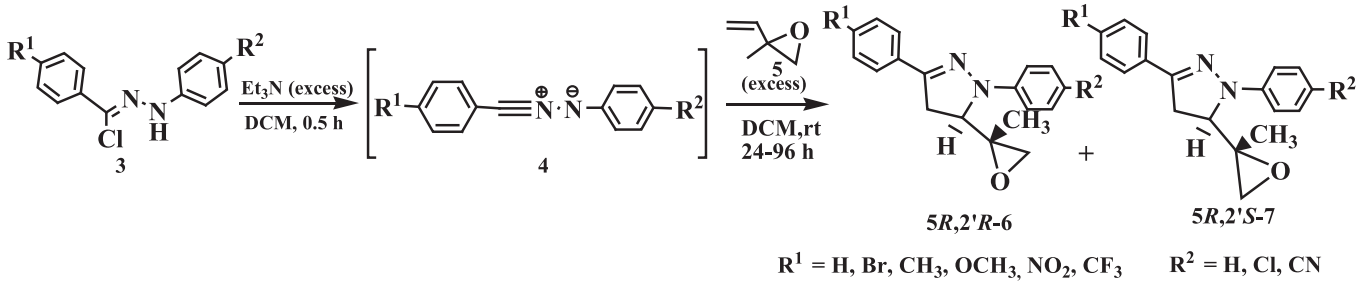
doi:10.1016/j.tet.2011.03.017



Scheme 1. Synthesis of 2-oxiranyl-4,5-dihydropyrazoles **6**–**7**.

After several trials for the optimization of the reaction conditions, the best yields and results were achieved by using 3 equiv of 2-methyl-2-vinyl oxirane and 8 equiv of triethylamine at room temperature in CH_2Cl_2 (Table 2). Although excess amount of triethylamine were used, it did not effect the formation of products in higher yields during the course of reaction.

Table 2
Optimization of reaction conditions to yield compounds **6**–**7**

Compd	Reaction conditions	Et_3N (equiv)	2M2VO (equiv)	Yield (%)
6a–**7a**	CH_3CN, reflux, 96 h	8	1.5	28
6a–**7a**	CH_3CN, rt, 120 h	2	1.0	28
6c–**7c**	CH_3CN, rt, 56 h	4	1.2	25
6c–**7c**	DCM, rt, 48 h	8	2.0	40
6c–**7c**	DCM, rt, 24 h	4	2.0	n.r
6h–**7h**	CH_3CN, rt, catalyst, 24 h	4	1.2	n.r

The structural elucidation of the cycloadducts, namely, 2-methyl-2-oxiranyl-substituted 4,5-dihydro-(*1H*)-pyrazoles (**6** and **7**) was performed by means of physical and spectroscopic methods, principally ^1H and ^{13}C, COSY and HSQC NMR, IR spectra, and HRMS measurements. Based on the chemical shifts and coupling constants of the aliphatic protons in proton NMR, concurrent formation of two diastereomers in nearly same amounts has been observed and exact ratio of diastereomers has been determined by comparing the integral values of aliphatic protons in crude reaction mixture, especially, methyl protons (Figs. 1 and 2). Only diastereomers **6c**–**7c**, **6e**–**7e**, and **6g**–**7g** could be separated from each other by chromatography and they were obtained as single diastereomers, the rest of cycloadducts yielded an inseparable diastereomeric mixture. Below, as a representative example, the partial proton NMR spectra of **6e** and **7e** indicating the aliphatic and methyl protons were shown (Fig. 1, Table 3). Among the aliphatic protons, Hc is the most deshielded one due to its proximity to nitrogen and the oxiranyl moiety and it appeared at around 4 ppm in both isomers as a doublet of doublets. The methylene protons of the oxirane ring (Hd and He) in both isomers resonated relatively upfield (2.60–2.80 ppm) with a J=4.6 Hz and these values are in accord with the literature report (Fig. 3).[21] The methylene protons of the pyrazoline ring (Ha and Hb), exhibited a typical ABX spin system with Hc as doublet of doublets with a J=17.1 and 12.8 Hz. The relationship between these protons can also clearly be seen in the COSY spectrum. In addition, the HSQC spectra confirmed that the connectivities of these protons to the carbons were also in accord

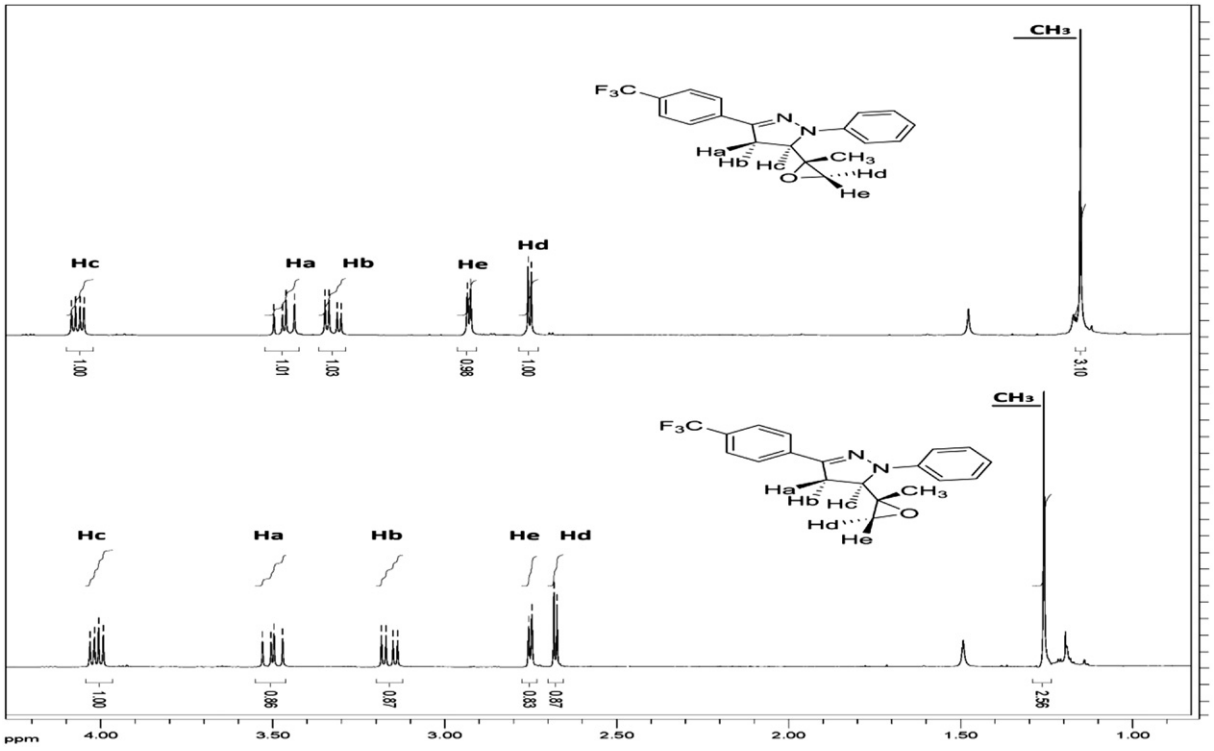


Fig. 1. Proton NMR splittings of the separated diastereomers **6e** and **7e**.

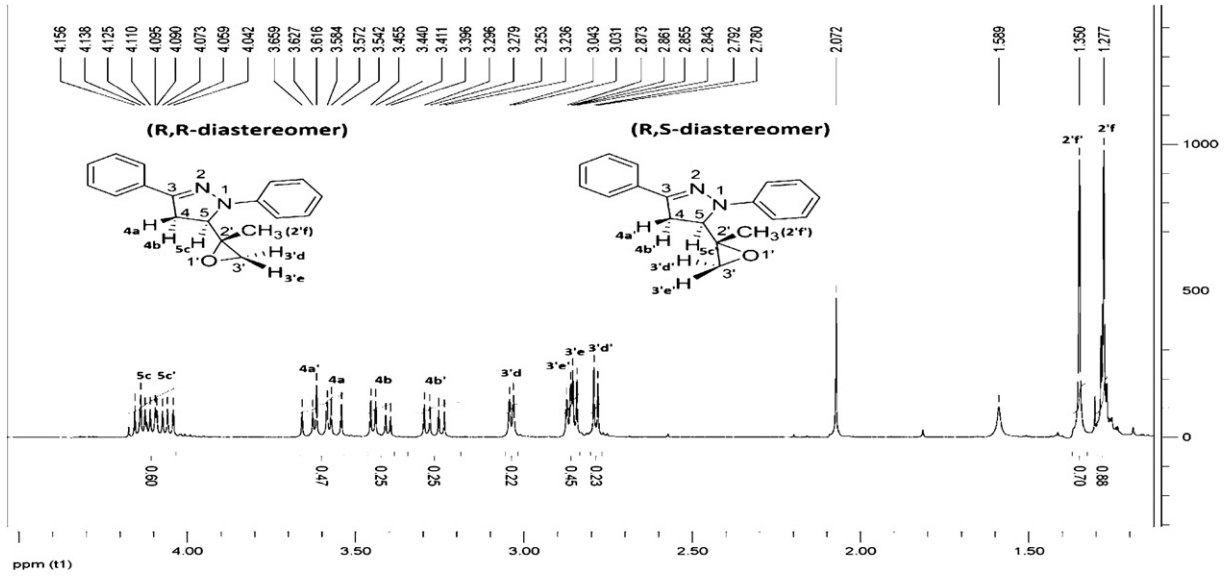
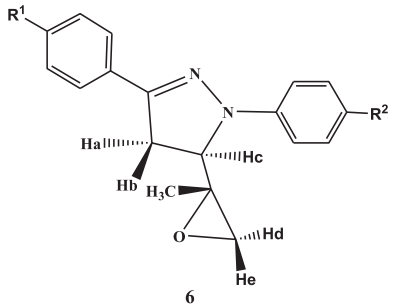


Fig. 2. Proton NMR splittings in the diastereomeric mixture of **6a** and **7a**.

Table 3
^{1}H NMR chemical shifts and couplings of the cycloadducts **6** and **7**



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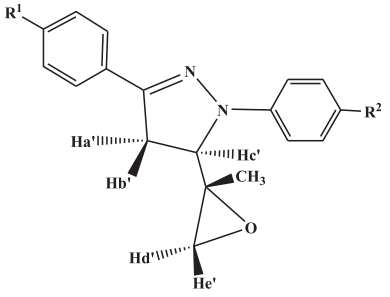

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Compd	R^1	R^2	Aromatic H δ (ppm)	Ha–Ha′ δ (ppm) J (Hz)	Hb–Hb′ δ (ppm) J (Hz)	Hc–Hc′ δ (ppm) J (Hz)	Hd–Hd′ δ (ppm) J (Hz)	He–He′ δ (ppm) J (Hz)	CH_3 δ (ppm)
6a–7a	H	H	7.76–6.87, 20H	3.54–3.61, dd, 17.4, 12.6; 3.62, d, 12.7	3.39–3.45, dd, 17.6, 5.8; 3.23–3.29, dd, 17.2, 6.6	4.09–4.13, dd, 11.3, 5.1; 4.04–4.09, dd, 12.7, 6.8	2.84, d, 4.7; 2.79, d, 4.7	3.03, d, 4.6; 2.87, d, 4.8	1.27, s 1.35, s
6b–7b	CH_3	H	7.56–6.78, 18H	3.42–3.49, dd, 17.3, 12.5; 3.54, dd, 12.6	3.27–3.33, dd, 17.6, 5.8; 3.11–3.17, dd, 17.2, 6.8	3.97–4.01, dd, 11.9, 5.8; 3.91–3.96, dd, 12.6, 6.8	2.74, d, 4.8; 2.68, d, 4.7	2.93, d, 4.7; 2.76, d, 4.8	2.31, s; 1.17, s; 1.24, s
6c	NO_2	H	8.27–7.86 9H	3.55–3.62, dd, 17.7, 12.2;	3.42–3.48, dd, 17.7, 5.9;	4.20–4.24, dd, 12.2, 5.9;	2.87, d, 4.6	3.04, d, 4.4	1.28, s
7c	NO_2	H	8.20–6.91, 9H	3.54–3.62, dd, 17.2, 13.0	3.21–3.27, dd, 17.2, 6.7	4.16–4.20, dd, 12.9, 6.6	2.74, d, 4.6	2.80, d, 4.6	1.35, s
6d–7d	CH_3O	H	7.61–6.77, 18H	3.41–3.53, td, 21.4, 12.5	3.26–3.32, dd, 17.6, 5.9; 3.11–3.17, dd, 17.1, 6.8	3.90–3.95, dd, 12.2, 6.5; 3.75, s, (OCH_3)	2.77, d, 4.7; 2.68, d, 4.7	2.94, d, 4.7; 2.75, d, 4.7	1.25, s; 1.18, s
6e	CF_3	H	7.75–6.83, 9H	3.44–3.50, dd, 17.6, 12.2;	3.31–3.35, dd, 17.6, 5.8;	4.05–4.09, dd, 12.2, 5.8;	2.75, d, 4.7	2.94, d, 4.7	1.16, s
7e	CF_3	H	7.73–6.82, 9H	3.49–3.55, dd, 17.2, 12.8	3.15–3.20, dd, 17.2, 6.8	4.02–4.06, dd, 12.8, 6.7	2.69, d, 4.8	2.76, d, 4.7	1.25, s
6f–7f	Br	Cl	7.50–7.02, 16H	3.42–3.54, td, 17.1, 12.7	3.25–3.31, dd, 17.6, 5.7; 3.10–3.16, dd, 17.3, 6.7	4.00–4.04, dd, 12.0, 5.6; 3.90–3.95, dd, 12.7, 6.7	2.74, d, 3.2; 2.68, d, 4.6	2.88, d, 4.6; 2.73, d, 3.2	1.16, s 1.20, s
6g	NO_2	Cl	8.18–7.07, 8H	3.48–3.54, dd, 17.5, 12.5	3.33–3.38, dd, 18.0, 6.0;	4.12–4.16, dd, 12.0, 5.5;	2.75, d, 4.5	2.90, d, 5.0	1.16, s
7g	NO_2	Cl	8.16–7.21, 8H	3.53–3.59, dd, 17.0, 13.0	3.17–3.22, dd, 17.0, 6.5	4.03–4.07, dd, 10.5, 6.5	2.75, d, 5.0	2.70, d, 5.0	1.21, s
6h–7h	CH_3	CN	7.56–7.08, 16H	3.51–3.59, m	3.30–3.35, dd, 17.7, 4.8; 3.15–3.20, dd, 17.4, 5.5	4.10–4.13, dd, 11.8, 4.8; 3.93–3.96, dd, 12.5, 5.7	2.74, d, 4.6; 2.70, d, 4.6	2.86, d, 4.6; 2.72, d, 4.6	2.30, s; 1.16, s 1.18, s

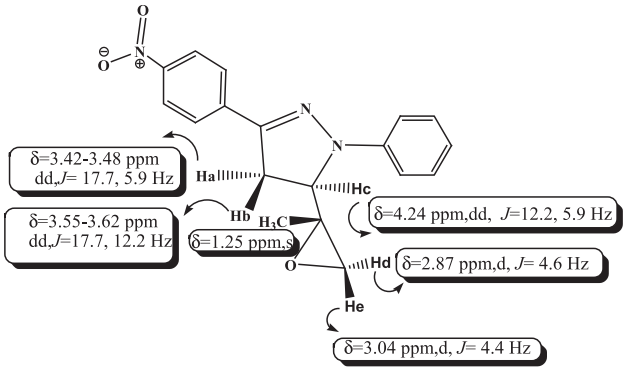


Fig. 3. Proton chemical shifts and couplings of **6c**.

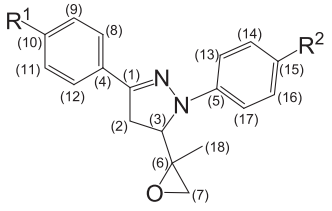
with the assigned structures. Thus, oxiranyl methylene protons (2.69 and 2.77 ppm) coincide with the carbon at 52.5 ppm. Pyrazoline ring methylene protons (Ha and Hb; 3.20 and 3.55 ppm) correlates with the carbon at 37.0 ppm.

The IR spectra of title compounds **6**–**7**(**a**–**h**) showed the C=N absorption bands around at 1593–1605 cm^{-1} and C–O–C absorption bands of oxirane rings around at 1100–1180 cm^{-1}. ^{13}C NMR spectra of all diastereomers showed that the C=N, iminic carbon resonated at around 140–150 ppm and oxirane methinic carbon at around 53–57 ppm (Table 4). EI and APCI-TOF-MS measurements gave the corresponding molecular ions. For some of the cycloadducts **6** or **7**, the base peaks were observed as either 1,3-disubstituted dihydro-1*H*-pyrazole species **8**, which is formed by the cleavage of oxirane ring from the cycloadducts or corresponding cyclopropene species **10** by the loss of nitrogen from pyrazole species formed and occasionally, base peaks were observed as saturated 2-methyl oxirane species **9** by loss of nitrilimine species (Scheme 2).

The diastereoselectivity of the reaction and configurations of the stereogenic centers of the cycloadducts **6c**, **7c**, and **7g** were established by single crystal X-ray diffraction (Fig. 4) and 2D-NMR spectra. Thus, nitrilimine cycloaddition to 2-methyl-2-vinyl oxirane are completely regioselective but yielded *R*,*R*-diastereomers as slightly major product among the two diastereomers formed by rotation of oxirane ring around single bond and it is obviously found that the diastereoselectivity of the reaction is low when the ratio of the diastereoisomers were compared (Table 1).

In addition to the synthesis of partially unsaturated cycloadducts, we have attempted to obtain fully aromatized pyrazoles for a deeper insight of the structures by conducting dehydrogenation reactions for the bridge protons by means of oxidizing agents, such as DDQ, chloranil, iodine pentoxide, in different reaction conditions according to the previously reported

Table 4
^{13}C NMR chemical shifts of the cycloadducts **6** and **7**



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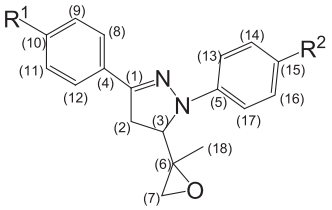

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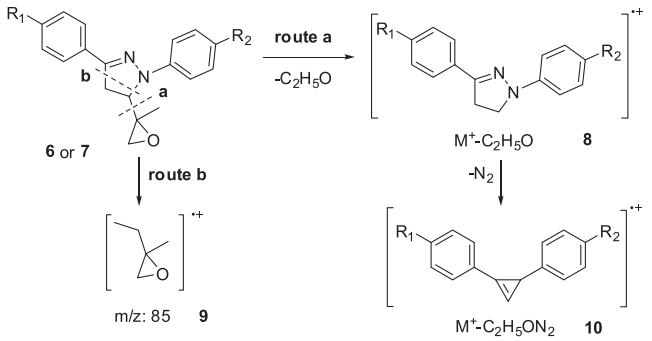
Compd	R^1	R^2	δ (ppm)														
			C1	C4	C5	C10	C14 (C16)	C9 (C11)	C8 (C12)	C15	C13 (C17)	C3	C6	C7	C2	C18	
6a	H	H	150.0,	137.4,	147.3,	129.5,	129.2,	129.0,	126.2,	119.9,	114.0,	65.8,	59.5,	56.7,	37.8,	16.6	
7a	H	H	148.3,	132.8,	145.7,	129.5,	129.1,	128.9,	126.1,	119.8,	113.8,	64.7,	58.6,	52.8,	37.6,	17.1	
6b	CH_3	H	156.0,	145.9,	150.0,	147.5,	129.7,	129.5,	126.2,	119.8,	114.0,	65.8,	59.5,	56.7,	37.9,	16.6,	21.8(CH_3)
7b	CH_3	H	155.7,	145.7,	148.5,	146.3,	129.6,	129.5,	126.1,	119.7,	113.7,	64.7,	58.6,	52.8,	37.7,	17.1,	21.7(CH_3)
6c	NO_2	H	143.9,	140.6,	135.3,	142.0,	126.1,	120.8,	122.4,	117.5,	110.8,	62.3,	54.7,	53.0,	33.4,	12.9	
7c	NO_2	H	143.2,	140.3,	135.0,	140.6,	125.6,	120.4,	122.2,	117.2,	110.2,	62.2,	56.2,	48.8,	34.2,	13.1	
6d	CH_3O	H	151.1,	132.8,	146.0,	161.0,	142.1,	113.9,	129.3,	119.7,	114.5,	65.7,	53.4,	50.0,	38.0,	16.7,	55.8 (OCH_3)
7d	CH_3O	H	150.0,	129.5,	142.3,	160.6,	139.9,	113.7,	128.5,	119.5,	114.4,	64.7,	52.9,	48.6,	34.7,	17.2,	56.7 (OCH_3)
6e	CF_3	H	146.1,	135.7,	144.5,	129.2,	125.7,	125.5,	125.5,	120.1,	113.8,	64.6,	58.0,	56.4,	36.9,	16.1,	125.4(CF_3)
7e	CF_3	H	145.1,	135.8,	144.7,	129.2,	125.7,	125.5,	125.5,	120.0,	113.6,	65.6,	58.9,	52.4,	37.0,	16.7,	125.5(CF_3)
6f	Br	Cl	147.7,	143.6,	143.9,	124.9,	129.5,	132.2,	127.7,	127.6,	115.2,	66.2,	59.3,	56.1,	37.8,	16.7	
7f	Br	Cl	146.6,	143.2,	143.8,	124.9,	129.4,	132.2,	127.7,	127.4,	115.0,	64.7,	58.3,	52.6,	37.6,	16.8	
6g	NO_2	Cl	147.3,	142.5,	138.2,	145.7,	129.2,	124.1,	126.0,	115.1,	110.5,	64.6,	57.7,	55.9,	36.8,	16.3	
7g	NO_2	Cl	147.2,	142.6,	138.3,	144.6,	129.2,	124.0,	125.9,	115.0,	110.2,	66.1,	58.8,	52.2,	37.0,	16.4	
6h	CH_3	CN	150.9,	133.5,	147.7,	139.9,	129.5,	128.9,	126.2,	100.8,	113.2,	65.2,	58.8,	55.0,	37.9,	15.8,	120.3 (C≡N), 21.4 (CH_3)
7h	CH_3	CN	149.8,	133.4,	147.6,	139.7,	129.4,	128.7,	126.1,	100.7,	113.0,	62.9,	57.7,	51.8,	37.6,	16.5,	120.2 (C≡N), 21.1 (CH_3)



Scheme 2. EI mass spectral fragmentation of cycloadducts **6**–**7**.

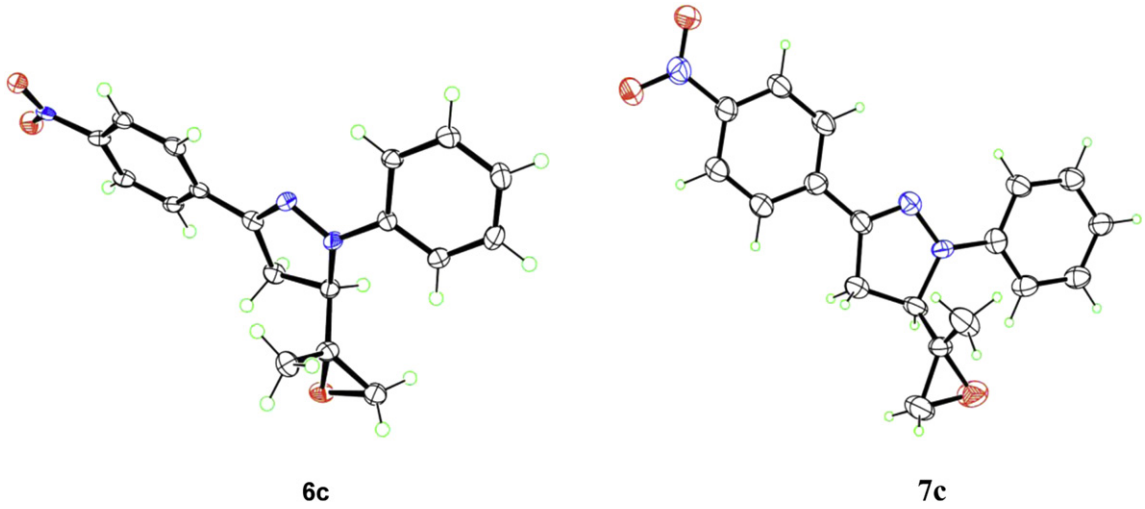


Fig. 4. X-ray ORTEP views of cycloadducts **6c** and **7c**.

methods[22–24] but all these experiments were unsuccessful and no aromatized cycloadducts could be obtained.

3. Conclusions

From the above results we demonstrated the regioselective formation of 5-oxiranyl substituted pyrazoles from nitrilimines and 2-methyl-2-vinyl oxirane (isoprene monoxide). No 4-oxiranyl substituted pyrazole cycloadducts were detected in the crude reaction mixture. In some cases, the diastereomers could not be separated. The structures were assigned by NMR and X-ray data. In conclusion, the present protocol introduces the first example of regio- and diastereoselective 1,3-dipolar cycloaddition of nitrilimines to 2-methyl-2-vinyl oxirane at room temperature and with simple purification.

4. Experimental section

4.1. General

^{1}H and ^{13}C NMR spectra were recorded on BRUKER and VARIAN spectrometers (400 and 500 MHz for proton and 100, 125 MHz for carbon) and all chemical shifts are reported in parts per million downfield from TMS. IR spectra were recorded on an SHIMADZU FTIR-8400S instrument (KBr pellet or NaCl discs). MALDI-Mass spectra were run on Bruker FTMS 4.7T BioAPEX II instrument and also high resolution mass spectra of the compounds were measured on a Bruker FTMS 4.7T BioAPEX II mass spectrometer. Single crystal X-ray Diffraction measurements were run on Enraf–Nonius CAD-4 Diffractometer. Chromatotron™ Centrifugal Thin-Layer Chromatograph System were used for isolation of final products. Melting points were determined on a MELTEMP apparatus and uncorrected. TLC was done using precoated plates with fluorescent indicator (Merck 5735). The stain solutions of permanganate, phosphomolybdic acid, and iodine were used for visualization of the TLC spots.

4.2. Synthesis of (*R*)-5-((*R*)-2-methyloxiran-2-yl)-1,3-disubstituted-4,5-dihydro-1*H*-pyrazoles or (*R*)-5-((*S*)-2-methyloxiran-2-yl)-1,3-disubstituted-4,5-dihydro-1*H*-pyrazoles (6–7). General procedure.

The corresponding hydrazonyl chloride **3** (0.5 mmol, 1.0 equiv) and Et_3N (2.0 mmol, 8 equiv) were dissolved in dry dichloromethane (20 mL) and stirred for 30 min. Then, isoprene monoxide **5** (1.5 mmol, 3.0 equiv) was added dropwise into the mixture and reaction mixture was stirred at room temperature under N_2 atmosphere. The progress of the reaction was monitored by TLC (20–96 h). After the reaction is complete, the reaction was concentrated and the reaction mixture was mixed and stirred with water (30 mL) to dissolve all the $Et_3N{\cdot}HCl$ salt and extracted by DCM (2×20 mL), dried over $MgSO_4$, and solvent was removed. Finally, the cycloadducts **6**–**7** were column chromatographed on silica gel (EtOAc–hexane) as either single isomer or a mixture of isomers.

*4.2.1. (R)-5-((R)-2-Methyloxiran-2-yl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (**6a**) and (R)-5-((S)-2-methyloxiran-2-yl)-1,3-diphenyl-4,5-dihydro-1H-pyrazole (**7a**). Two inseparable diastereomers. Compounds* **6a**–**7a**: Orange oily solid (110 mg, 92%). Melting range: 82–87 °C. R_f: 0.55–0.45 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3057, 2983 (C–H), 2926, 1600 (C=N), 1552, 1500, 1394, 1323, 1124, 883, 758,750 cm^{-1}. TOF-MS EI^+: (*m*/*z*, %)=278 (15) $[M]^+$, 221 (50), 176 (20), 105 (90), 85 (100). HRMS calculated for $C_{18}H_{18}N_2O$ 278.1419; found 278.1417.

*4.2.2. (R)-5-((R)-2-Methyloxiran-2-yl)-1-phenyl-3-p-tolyl-4,5-dihydro-1H-pyrazole (**6b**) and (R)-5-((S)-2-methyloxiran-2-yl)-1-phenyl-3-p-tolyl-4,5-dihydro-1H-pyrazole (**7b**). Two inseparable diastereomers. Compounds* **6b**–**7b**: White needles (117 mg, 80%). Melting range: 92–98 °C. R_f: 0.50–0.45 (ethyl acetate–*n*-hexane;

1:4). IR (KBr): ν=3036, 2922 (C–H), 2852, 1597 (C=N), 1500, 1390, 1325, 1124, 815, 748 cm^{-1}. TOF-MS EI$^+$: (*m*/*z*, %)=292 (30) $[M]^+$, 272 (15), 235 (100), 77 (20). HRMS calculated for $C_{19}H_{20}N_2O_3$ 292.1576; found 292.1578.

*4.2.3. (R)-5-((R)-2-Methyloxiran-2-yl)-3-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**6c**) and (R)-5-((S)-2-methyloxiran-2-yl)-3-(4-nitrophenyl)-1-phenyl-4,5-dihydro-1H-pyrazole (**7c**). Two separated diastereomers. Compound* **6c**: Light orange needles (from diisopropylphenylether–acetone) (30 mg, 20%). Mp 155–157 °C. R_f: 0.75 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3047, 2924 (C–H), 2850, 1593 (C=N), 1552, 1500, 1340, 1107, 846, 752 cm^{-1}. TOF-MS EI$^+$: (*m*/*z*, %)=323 (35) $[M]^+$, 266 (90), 235 (95), 83 (100). HRMS calculated for $C_{18}H_{17}N_3O_3$ 323.1270; found 323.1276. *Selected crystallographic data*: $C_{18}H_{17}N_3O_3$ *F*(000)=680, M_r=323.35, D_x=1.392 Mg m^{-3}. Monoclinic, *P*21/*c* Cu *K*α radiation, λ=1.54178 Å. Hall symbol: −*P* 2 ybc. Cell parameters from 3237 reflections *a*=17.0933 (9) Å, θ=5.1–67.6°, *b*=9.9259 (5) Å, μ=0.79 mm^{-1}, *c*=9.3363 (4) Å, *T*=90 K, β=103.091 (3)°. Plate, Orange *V*=1542.89 (13) $Å^3$, 0.24×0.21×0.05 mm, *Z*=4. *Data collection* Bruker APEX-II CCD diffractometer 8539 independent reflections. Radiation source: fine-focus sealed tube 6947 reflections with $I>2\sigma(I)$ graphite R_{int}=0.0000φ and ω scans θ_{max}=69.3°, θ_{min}=5.1°. Absorption correction: Multi-scan *SADABS* (Sheldrick, 2002) *h*=−20→20T_{min}=0.832, T_{max}=0.961, *k*=−11→118,539 measured reflections *l*=−8→10.

Compound **7c**: Dark orange needles (from diisopropylphenylether–acetone) (25 mg, 20%). Mp 152–154 °C. R_f: 0.62 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3059, 2926 (C–H), 2854, 1593 (C=N), 1552, 1502, 1340, 1107, 846, 752 cm^{-1}. TOF-MS EI$^+$: (*m*/*z*, %)=323 (5) $[M]^+$, 289 (20), 273 (40), 235 (100), 83 (100). HRMS calculated for $C_{18}H_{17}N_3O_3$ 323.1270; found 323.1269. *Selected crystallographic data*: $C_{18}H_{17}N_3O_3$ *Z*=2, M_r=323.35, *F*(000)=340. Triclinic, *P*1 D_x=1.391 Mg m^{-3}. Hall symbol: −P 1 Cu *K*α radiation, λ=1.54178 Å, *a*=6.2053 (7) Å. Cell parameters from 891 reflections *b*=10.8579 (12) Å, θ=3.7–56.9°, *c*=11.8305 (14) Å, μ=0.79 mm^{-1}, α=98.431 (9)°, *T*=90 K, β=91.549 (9)°. Fragment, Orange γ=101.223 (9)° 0.13×0.10×0.04 mm, *V*=772.14 (15) $Å^3$. *Data collection* Bruker APEX-II CCD diffractometer 2186 independent reflections. Radiation source: fine-focus sealed tube 1086 reflections with $I>2\sigma(I)$ graphite R_{int}=0.118φ and ω scans θ_{max}=59.1°, θ_{min}=3.7°. Absorption correction: Multi-scan *SADABS* (Sheldrick, 2002) *h*=−5→6 T_{min}=0.904, T_{max}=0.969, *k*=−9→126,710 measured reflections *l*=−12→13.

*4.2.4. (R)-3-(4-Methoxyphenyl)-5-((R)-2-methyloxiran-2-yl)-1-phenyl-4,5-dihydro-1H-pyrazole (**6d**) and (R)-3-(4-methoxyphenyl)-5-((S)-2-methyloxiran-2-yl)-1-phenyl-4,5-dihydro-1H-pyrazole (**7d**). As a mixture of two inseparable diastereomers. Compounds* **6d**–**7d**: Brown oil (75 mg, 65%). R_f: 0.75–0.65 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3049, 2931 (C–H), 2837, 1597 (C=N), 1500, 1390, 1251, 1172, 833, 748 cm^{-1}. TOF-MS EI$^+$: (*m*/*z*, %)=308 (55) $[M]^+$, 251 (100), 235 (80), 207 (50). HRMS calculated for $C_{19}H_{20}N_2O_2$ 308.1525; found 308.1522.

*4.2.5. (R)-5-((R)-2-Methyloxiran-2-yl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole (**6e**) and (R)-5-((S)-2-methyloxiran-2-yl)-1-phenyl-3-(4-(trifluoromethyl)phenyl)-4,5-dihydro-1H-pyrazole (**7e**). Two separated diastereomers. Compound* **6e**: Light green powder (50 mg, 44%). Mp 118–120 °C. R_f: 0.44 (ethyl acetate–*n*-hexane; 1:4). IR (KBr): ν=3055, 2928 (C–H), 2848, 1599 (C=N), 1498, 1325, 1122, 1066, 840, 748 cm^{-1}. TOF-MS AP$^+$: (*m*/*z*, %)=347 (100) $[MH]^+$, 348 (25) $[MH]^+$, 318 (15), 289 (15). HRMS calculated for $C_{19}H_{18}N_2OF_3$ 347.1371; found 347.1375.

Compound **7e**: Light green oil (45 mg, 40%). R_f: 0.33 (ethyl acetate–*n*-hexane; 1:4). IR (KBr): ν=3061, 2928 (C–H), 2854, 1593 (C=N), 1599, 1500, 1325, 1124, 1066, 842, 750 cm^{-1}. TOF-MS AP$^+$: (*m*/*z*, %)=347 (100) $[MH]^+$, 348 (25) $[MH]^+$. HRMS calculated for $C_{19}H_{18}N_2OF_3$ 347.1371; found 347.1371.

*4.2.6. (R)-3-(4-Bromophenyl)-1-(4-chlorophenyl)-5-((R)-2-methyloxiran-2-yl)-4,5-dihydro-1H-pyrazole (**6f**) and (R)-3-(4-bromophenyl)-1-(4-chlorophenyl)-5-((S)-2-methyloxiran-2-yl)-4,5-dihydro-1H-pyrazole (**7f**). Two inseparable diastereomers. Compounds* **6f**–**7f**: White needles (108 mg, 95%). Melting range: 126–128 °C. R_f: 0.40–0.30 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3049, 2922 (C–H), 2850, 1597 (C=N), 1490, 1386, 1093, 1006, 821 cm^{-1}. TOF-MS AP$^+$: (*m*/*z*, %)=391 (80) $[M]^+$, 393 (100) $[M]^+$+2. HRMS calculated for $C_{18}H_{17}N_2OClBr$ 391.0213; found 391.0216.

*4.2.7. (R)-1-(4-Chlorophenyl)-5-((R)-2-methyloxiran-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole (**6g**) and (R)-1-(4-chlorophenyl)-5-((S)-2-methyloxiran-2-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole (**7g**). Two separated diastereomers. Compound* **6g**: Light orange needles (40 mg, 24%). Mp 195–197 °C. R_f: 0.60 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3109, 3039, 2912 (C–H), 2848, 1593 (C=N), 1496, 1342, 1109, 819, 752 cm^{-1}. TOF-MS EI$^+$: (*m*/*z*, %)=357 (25) $[M]^+$, 327 (30), 300 (60), 269 (100). HRMS calculated for $C_{18}H_{16}N_3O_3Cl$ 357.0880; found 357.0876.

Compound **7g**: Orange-red needles (60 mg, 35%). Mp 189–191 °C. R_f: 0.45 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3064, 2924 (C–H), 2856, 1593 (C=N), 1491, 1338,1323, 1141, 1097, 848, 821, 748 cm^{-1}. TOF-MS EI$^+$: (*m*/*z*, %)=357 (25) $[M]^+$, 327 (40), 300 (60), 270 (100). HRMS calculated for $C_{18}H_{16}N_3O_3Cl$ 357.0880; found 357.0877.

*4.2.8. 4-((R)-5-((R)-2-Methyloxiran-2-yl)-3-p-tolyl-4,5-dihydro-1H-pyrazol-1-yl) benzonitrile (**6h**) and 4-((R)-5-((S)-2-methyloxiran-2-yl)-3-p-tolyl-4,5-dihydro-1H-pyrazol-1-yl)benzonitrile (**7h**). Two inseparable diastereomers.* Brown powder (75 mg, 65%). Melting range: 137–145 °C. R_f: 0.22–0.11 (ethyl acetate–*n*-hexane; 1:2). IR (KBr): ν=3049, 2922 (C–H), 2860, 2214 (C≡N), 1605 (C=N), 1510, 1398, 1332, 1174, 827 cm^{-1}. TOF-MS AP$^+$: (*m*/*z*, %)=318 (100) $[M]^+$, 359 (30) $[M]^+$+K. HRMS calculated for $C_{20}H_{20}N_3O$ 318.1606; found 318.1620.

5. Supplementary data

Full crystallographic data for **7c** and **6c** have been deposited with the CCDC reference numbers 798327, 797328, respectively, and can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

Abant İzzet Baysal University, Directorate of Research Projects Commission (BAP grant no. 2007.03.03.260) and TUBITAK (Turkish Scientific and Technological Research Council) (grant no. 106T645) are gratefully acknowledged for financial support.

The authors also thank to Professor D.W. Knight (School of Chemistry, Cardiff University, U.K.) for HRMS measurements and Dr. F.R. Fronczek (Department of Chemistry, Louisiana State University, U.S.A.) for X-Ray data.

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