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PAPER

Novel one-pot process for the synthesis of 1,3-thiazoles *via* organocatalysed epoxidation of nitro-olefins†

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A facile one-pot two-step process for the synthesis of 1,3-thiazole heterocycles *via* organocatalytic epoxidation of nitro-olefins with the *t*-BuOOH/DBU system, and subsequent reaction of α-nitro-epoxides with thioamides under mild conditions has been developed.

Introduction

Thiazoles are of eminent importance because of their potential as bioactive compounds[1,2] and versatile building blocks for natural products and pharmaceuticals.[3,4] Thiazole heterocycles are important subunits in many complex natural compounds and drugs, *e.g.* Vitamine B1, Epothilones, Thiostrepton, Nizatidine (ulcer therapeutic), Ritonavir (a potent inhibitor of HIV protease) (Fig. 1) and thiamine pyrophosphate (TPP, a coenzyme that is part of the Krebs cycle in the process of cellular respiration).[3–6] Further, there are many other applications of thiazole derivatives, for example in liquid crystals[7] or cosmetics (sunscreens).[8]

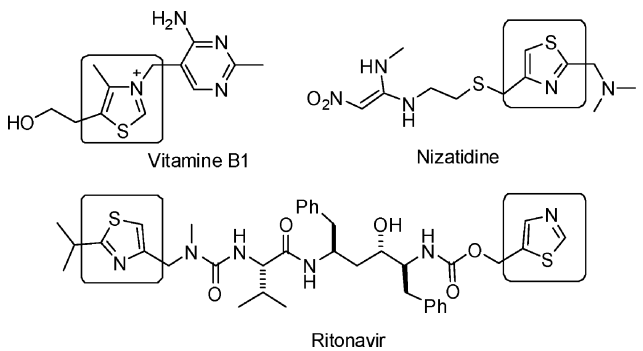

Fig. 1 Thiazoles as part of natural compounds and drugs.

The most prominent method to synthesize thiazoles is the Hantzsch thiazole synthesis where α-haloketones are reacted with thioamides.[9] Several other multi-step[5] and also some multicomponent syntheses[10] are known. One of the less explored methods is to prepare thiazoles from the corresponding epoxides (*e.g.* 2-chlorooxiranes, α-nitro-epoxides) and thioamides or thioureas.[11] This is surprising, since epoxides are particularly attractive intermediates and building blocks for the synthesis of complex organic molecules, *e.g.* of natural products and biologically active compounds.[12] Diverse approaches to catalytic epoxidations have been developed in recent years.[13] Notably, the thiazole synthesis from the corresponding α-nitro-epoxides (generated from nitro-olefins with H_2O_2/NaOH system) was first reported by Newman.[11a,b] However, as far as we are aware, this has been the only example of preparation and application of α-nitro-epoxides for the thiazole synthesis (heating a mixture of α-nitro-epoxide and thiobenzamide under reflux in MeOH for 16 h). Therefore, the development of new efficient procedures for the synthesis of α-nitro-epoxides and their use for the preparation of thiazole heterocycles still remains a challenging task.

As a continuation of our interest in organocatalytic epoxidation reactions,[14] we decided to develop an organocatalytic epoxidation of nitro-olefins with an intention to further apply the corresponding products, α-nitro-epoxides, without workup and purification for the synthesis of 1,3-thiazoles. Herein, we disclose a novel and practical approach to thiazole derivatives: one-pot two-step synthesis, which involves an organocatalytic epoxidation of nitro-olefins with *t*-BuOOH/DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) system, followed by reaction with different thiobenzamides at room temperature.

Results and discussion

Notably, one-pot processes are very attractive and sustainable methods in modern synthetic chemistry through the reduction of work-up and purification steps, reduction of costs, materials and labor input.[15] In view of our idea to develop a one-pot procedure towards thiazole synthesis, we first studied the epoxidation of β-methyl-β-nitrostyrene **1**. In 1995, Yadav reported the epoxidation of α,β-unsaturated-δ-lactones and other enones using anhydrous TBHP (*t*-BuOOH) as an oxidant and DBU as a base (at 120 mol% loading) at 0 °C.[16] We decided to extend the application of this readily available system to the epoxidation of more challenging

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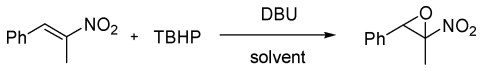
Table 1 Catalytic epoxidation of *trans*-*β*-methyl-*β*-nitrostyrene **1** with TBHP/DBU system



1 (1.0 eq.) 2.0 eq. **2**

Entry	DBU (mol%)	Temp	Solvent	t (min)	Conv. (%)[a]
1	20	0 °C	n-Hexane	135	90
2	20	rt	n-Hexane	45	90
3	**5**	**rt**	**n-Hexane**	**50**	**90**
4	5	rt	Toluene	85	78
5	5	rt	$CHCl_3$	85	55
6	5	rt	EtOH	60	38
7	5	rt	MeOH	60	25[b]

[a] Conversions were determined by GC analysis based on the formation of epoxide. The reaction was monitored until consumption of the alkene. [b] Conversion was determined by ^{1}H NMR analysis using an internal standard.

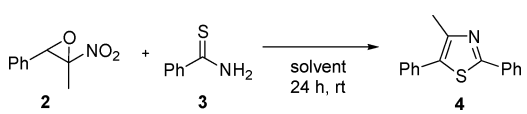
nitro-olefins. Following our aim to develop a catalytic epoxidation of *β*-methyl-*β*-nitrostyrene **1**, we used catalytic amounts of DBU (at 5–20 mol% loading) for optimization of reaction conditions (Table 1).

In a typical procedure, TBHP was added to a mixture containing **1** in n-hexane, DBU and an internal standard (hexadecane). The mixture was stirred and the progress of the reaction was monitored by GC. To our delight, we found that DBU is indeed an efficient catalyst for the epoxidation of **1** with TBHP as oxidant. Intriguingly, while 90% conv. was observed after 135 min at 0 °C, the same conversion was observed in only 45 min at room temperature, using DBU at 20 mol% loading in both reactions (entries 1 and 2). We further reduced the catalyst loading to 5 mol% without loss in activity with a slightly extended reaction time (50 min, entry 3). Among various solvents screened, the originally chosen n-hexane proved to be the most optimal solvent (entry 3 *vs.* entries 4–7).

Next, the optimal conditions for the thiazole formation from epoxide **2** and thiobenzamide **3** were investigated (Table 2). First, the thiazole synthesis was conducted under the conditions found for the epoxidation step: in n-hexane as a solvent and at room temperature (entry 1).

In this case, **4** was isolated only in 34% yield. Applying the same solvent (MeOH) as reported in the literature,[11a,b] but carrying out the reaction at room temperature instead of under reflux conditions, the desired product was isolated in 62% yield (entry 2). To improve the yield, the amount of **3** was increased to 2.0 equiv.

Table 2 Optimization of conditions for the thiazole formation

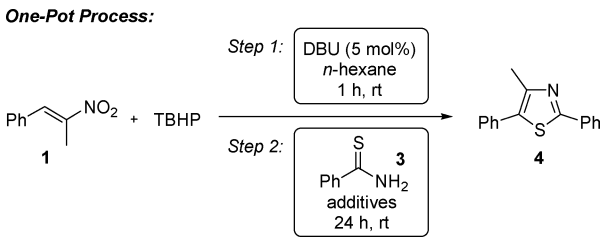


2 **3** **4**

Entry	Solvent	**3** (equiv.)	Yield[a] (%)
1	n-Hexane	1.0	34
2	MeOH	1.0	62
3	n-Hexane	2.0	66
4	MeOH	2.0	80

[a] Yield of the isolated product after column chromatography.

Table 3 Optimization of the one-pot process



1 **4**

Step 1:		*Step 2*:		
Entry	TBHP (equiv.)	**3** (equiv.)	Add. (equiv.)	Yield[a] (%)
1	2.0	2.0	—	34
2	1.0	1.0	—	22
3	2.0	1.0	—	25
4	1.0	2.0	—	56
5	1.0	2.0	MeOH (100)	56
6	1.0	2.0	AcOH (0.1)	60
7	1.0	2.0	AcOH (0.5)	56
8	1.0	2.0	MeOH (100) AcOH (0.1)	63
9	1.0	2.0	TFA (0.1)	70
10	1.0	2.0	MeOH (100) TFA (0.1)	51

[a] Yield of the isolated product after column chromatography.

using n-hexane (entry 3) and MeOH (entry 4) as solvents. In both cases, the yield was improved to 66% and 80%, respectively.

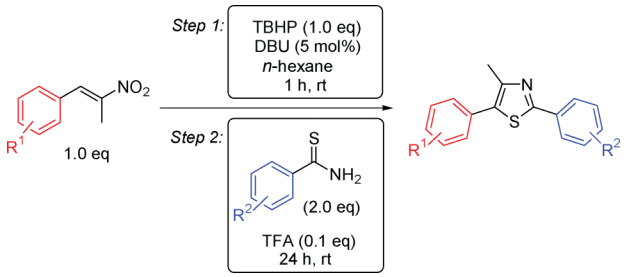
The next aim was to combine the optimized conditions of the two single reaction steps (for the epoxidation reaction and the formation of thiazole) in one-pot (Table 3). We started our investigation of the one-pot process by simply adding 2.0 equiv. of thiobenzamide **3** after 1 h reaction time for the epoxidation that was conducted in n-hexane (entry 1). Surprisingly, the thiazole product **4** was isolated in only 34% yield. Reduction of the amount of **3** from 2.0 to 1.0 equiv. resulted in decreased yields (entries 2 and 3). To our delight, by perfoming the epoxidation with 1.0 equiv. of TBHP followed by the addition of 2.0 equiv. of **3**, we were able to isolate **4** in 56% yield (entry 4).

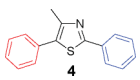
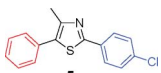
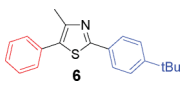
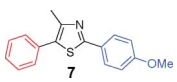
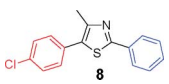
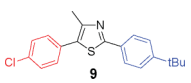
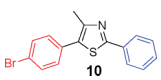
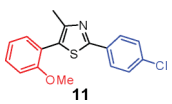
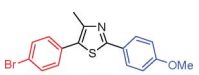
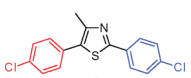
Motivated by this result, we hoped to improve the yield further by using additives in the second step of the one-pot process. MeOH came to our mind, because as shown in Table 2, the formation of **4** was very efficient in this solvent (entry 4, Table 2). Thus, MeOH was added to the second step of the one-pot process in 100 equiv. with no improvement in the yield (entry 5, Table 3). Addition of 0.1 equiv. of acetic acid led to 60% yield (entry 6) and the use of both additives, MeOH and acetic acid gave 63% yield (entry 8). Finally, trifluoroacetic acid (TFA) was tested to provide the isolated product in 70% yield after two sequential steps (entry 9). However, the combination of TFA with MeOH gave a lower yield (entry 10).

We next examined the scope of the one-pot two-step process for different nitroalkenes and thiobenzamides using the optimized reaction conditions. The results are summarized in Table 4.

To our delight, all reactions investigated can be effected in 40–70% yield, applying DBU at only 5 mol% loading. Generally, higher yields (65–70%) were obtained using **1** as alkene and thiobenzamides with R^2 = H, electron withdrawing or neutral substituents (entries 1–3). Interestingly, the reaction conditions

Table 4 Scope of substrates



Entry[a]	R^1	R^2	Product	Yield (%)[b]
1	H	H	 4	70
2	H	*p*-Cl	 5	65
3	H	*p*-*t*Bu	 6	65
4	H	*p*-OMe	 7	41
5	*p*-Cl	H	 8	50
6	*p*-Cl	*p*-*t*Bu	 9	48
7	*p*-Br	H	 10	52
8	*o*-OMe	*p*-Cl	 11	40
9	*p*-Br	*p*-OMe	 12	51
10	*p*-Cl	*p*-Cl	 13	40

[a] One-pot conditions from Table 3, entry 9 were used for entries 1–4. One-pot conditions from Table 3, entry 10 were used for entries 5–10. [b] Isolated yield after column chromatography.

from Table 3, entry 10 (MeOH/TFA as additives) proved to be better suitable for olefines with R^1 = electron withdrawing and/or donating group (entries 5–10, Table 4).

Conclusion

In summary, a novel one-pot process providing a practical route for the formation of 1,3-thiazoles from nitro-olefins was developed.

The use of commercially available DBU as an organocatalyst for the epoxidation of nitro-olefins with TBHP, followed by the reaction with thiobenzamides, and the very mild conditions used for both transformations, make this process a simple and convenient approach to obtain thiazole heterocycles.

Experimental

General information

Chemicals were used as received from common commercial sources. All solvents were distilled before use. *n*-Hexane (HPLC grade) was obtained from Fisher Scientific and used as received. NMR spectra were recorded on Jeol (400 and 400) or Bruker Avance (300 or 400). NMR spectra were referenced to the residual solvent signal (^{1}H: $CDCl_3$, 7.24 ppm; ^{13}C: $CDCl_3$, 77.0 ppm) and recorded at ambient probe temperature. IR spectra were recorded as thin films on a Varian IR-660 spectrometer. FAB mass spectra were measured with a Micromass ZabSpec, EI mass spectra were recorded with a Finnigan MAT 95 XP spectrometer. Gas chromatography (GC) was conducted on a Thermo instrument Trace GC Ultra with a 7 m TR5 column. Thin-Layer chromatography (TLC) was carried out on ALUGRAM® SIL G/UV254 (Macherey-Nagel) and visualized by UV. Flash column chromatography was performed using silica gel 60 M (Macherey-Nagel).

General procedure for the one-pot two-step synthesis of thiazoles

A round bottom flask was charged with *trans*-*β*-methyl-*β*-nitrostyrene (0.028 g, 0.170 mmol), DBU (1.3 µL, 0.008 mmol) and n-hexane (0.56 mL). Then TBHP (34.1 µl, 0.170 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h. Then thiobenzamide (0.047 g, 0.340 mmol) and TFA (1.3 µl, 0.017 mmol) were added and the reaction mixture was stirred for 24 h. The crude product was extracted with Et_2O and purified by column chromatography (SiO_2, PE/EtOAc 97 : 3) to yield a white solid.

4-Methyl-2,5-diphenylthiazole (4)[17]

White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.92 (m, 2H), 7.49–7.32 (m, 8H), 2.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 148.8, 133.7, 132.2, 129.8, 129.1, 128.9, 128.7, 127.7, 126.3, 16.4. MS (FAB) *m*/*z*: 252 (100%, M + H$^+$).

2-(4-Chlorophenyl)-4-methyl-5-phenylthiazole (5)[17]

White solid. Mp 114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.88–7.84 (m, 2H), 7.48–7.35 (m, 7H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 149.0, 135.7, 132.6, 132.2, 131.9, 129.1, 129.1, 128.7, 127.9, 127.4, 16.3. IR (thin film): 2922, 2360, 1653, 1600, 1572, 1534 cm^{-1}. MS (EI) *m*/*z*: 285 (100%, M$^+$); HRMS (EI): Calc. for $C_{16}H_{12}ClNS$: 285.0379; Found: 285.0372. Anal. Calc. for $C_{16}H_{12}ClNS$: C, 67.24; H, 4.23; N, 4.90; S, 11.22. Found: C, 66.78; H, 4.55; N, 4.67; S, 12.41.

2-(4-(*tert*-Butyl)phenyl)-4-methyl-5-phenylthiazole (6)

White solid. Mp 109 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 8.4 Hz, 2H), 7.50–7.39 (m, 6H), 7.36–7.31 (m, 1H), 2.55

(s, 3H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.3, 153.3, 148.7, 132.4, 131.8, 131.1, 129.2, 128.7, 127.7, 126.1, 125.9, 34.8, 31.1, 16.3. IR (thin film): 3058, 2961, 2868, 1773, 1736, cm^{-1}. MS (EI) *m/z*: 307 (85%, M^+), 292 (100, M – CH_3); HRMS (EI): Calc. for $C_{20}H_{21}NS$: 307.1395; Found: 307.1408. Anal. Calc. for $C_{20}H_{21}NS$: C, 78.13; H, 6.88; N, 4.56; S, 10.43. Found: C, 78.32; H, 6.98; N, 4.55; S, 10.20.

2-(4-Methoxyphenyl)-4-methyl-5-phenylthiazole (7)

White solid. Mp 63 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, *J* = 9.2 Hz, 2H), 7.48–7.24 (m, 5H), 6.94 (d, *J* = 9.2 Hz, 1H), 3.84 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.0, 161.0, 148.4, 132.4, 131.2, 129.1, 128.7, 127.7, 127.6, 126.7, 114.2, 55.4, 16.4. IR (thin film): 3001, 2960, 2931, 2853, 1604, 1574, 1559, 1515 cm^{-1}. MS (EI) *m/z*: 281 (100%, M^+); HRMS (EI): Calc. for $C_{17}H_{15}NOS$: 281.0874; Found: 281.0874. Anal. Calc. for $C_{17}H_{15}NOS$: C, 72.57; H, 5.37; N, 4.98; S, 11.40. Found: C, 72.50; H, 5.72; N, 5.29; S, 11.25.

5-(4-Chlorophenyl)-4-methyl-2-phenylthiazole (8)[17]

White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.90 (m, 2H), 7.43–7.39 (m, 7H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 148.7, 133.3, 133.0, 130.4, 130.2, 129.9, 129.5, 125.9, 15.9. MS (EI) *m/z*: 285 (100%, M^+), 182 (75); HRMS (EI): Calc. for $C_{16}H_{12}ClNS$: 285.0379; Found: 285.0389.

2-(4-(*tert*-Butyl)phenyl)-5-(4-chlorophenyl)-4-methylthiazole (9)

White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.83 (d, *J* = 9.0 Hz, 2H), 7.45–7.39 (m, 6H), 2.52 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.0, 152.9, 148.5, 133.2, 130.4, 130.3, 129.9, 128.4, 125.6, 125.4, 34.4, 30.7, 15.9. MS (EI) *m/z*: 341 (100%, M^+); HRMS (EI): Calc. for $C_{20}H_{20}ClNS$: 341.1005; Found: 341.0993. Anal. Calc. for $C_{20}H_{20}ClNS$: C, 70.26; H, 5.90; N, 4.10; S, 9.38. Found: C, 69.67; H, 6.35; N, 4.05; S, 9.39.

5-(4-Bromophenyl)-4-methyl-2-phenylthiazole (10)

White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.90 (m, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.43–7.24 (m, 5H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 161.8, 148.7, 133.0, 131.4, 130.7, 130.2, 129.5, 128.5, 125.8, 15.9. MS (EI) *m/z*: 329 (100%, M^+); HRMS (EI): Calc. for $C_{16}H_{12}BrNS$: 328.9782; Found: 328.9797. Anal. Calc. for $C_{16}H_{12}BrNS$: C, 58.19; H, 3.66; N, 4.24; S, 9.71. Found: C, 57.82; H, 4.22; N, 4.10; S, 10.07.

2-(4-Chlorophenyl)-5-(2-methoxyphenyl)-4-methylthiazole (11)

White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.4 Hz, 2H), 7.39–7.31 (m, 4H), 7.04–6.97 (m, 2H); 3.84 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.0, 156.5, 150.4, 135.0, 132.0; 131.5, 129.4, 128.6, 127.5, 127.0, 120.1, 120.0, 110.7, 55.1, 15.9. IR (thin film): 3002, 2958, 2919, 2831, 1581, 1537 cm^{-1}. MS (EI) *m/z*: 315 (100%, M^+); HRMS (EI): Calc. for $C_{17}H_{14}ClNOS$: 315.0485; Found 315.0467.

5-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-methylthiazole (12)

White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 9.0 Hz, 2H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9, 160.6, 148.4, 131.4, 130.8, 130.1, 129.4, 127.3, 126.0, 121.3, 113.8, 55.0, 15.9. MS (EI) *m/z*: 358 (100%, M^+); HRMS (EI) Calc. for $C_{17}H_{14}ONBrS$: 358.9979, Found: 358.9993. Anal. Calc. for $C_{17}H_{14}ONBrS$: C, 56.67; H, 3.92; N, 3.89; S, 8.90, Found: C, 56.32; H, 3.92; N, 3.87; S, 9.00.

2,5-Bis(4-chlorophenyl)-4-methylthiazole (13)

White solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 9.0 Hz, 2H), 7.40–7.37 (m, 6H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.1, 149.5, 136.0, 134.1, 132.2, 131.4, 130.6, 130.5, 129.1, 127.6, 16.5. MS (EI) *m/z*:, 320 (20%, M^+), 321 (80), 319 (100); HRMS (EI) Calc. for $C_{16}H_{11}Cl_2NS$: 318.9989, Found: 318.9931. Anal. Calc. for $C_{16}H_{11}Cl_2NS$: C, 60.01; H, 3.46; N, 4.37; S, 10.01, Found: C, 59.51; H, 3.27; N, 4.34; S, 10.27.

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