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ORIGINAL ARTICLE

Ultrasound-promoted synthesis of novel fused heterocycles by criss-cross cycloaddition

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Abstract This work reports a novel and highly efficient methodology for the synthesis of perhydrotriazolotriazoledithions from two successive 1,3-dipolar cycloaddition under ultrasound irradiation. Aromatic 2,3-diazabuta-1,3-diene ligands with thiocyanates in glacial AcOH produced the corresponding perhydro [1,2,4] triazolo [1,2-*a*] [1,2,4] triazole-1,5-dithiones via criss-cross cycloaddition reactions under ultrasound irradiation. Structures of all compounds were characterized by ^{1}H and ^{13}C NMR, UV, IR and elemental analysis spectral data. The major advantages of the reported method are its selectivity, operational simplicity, extremely mild reaction conditions, short reaction times, and excellent yields.

1. Introduction

Due to increasing environmental consciousness in chemical research and industry, the challenge for a sustainable environment calls for clean procedures (Doble and Kumar, 2007). Ultrasonic-assisted organic synthesis (UAOS) as an environment-friendly synthetic approach is a powerful technique that is being used more and more to accelerate organic reactions (Xu et al., 2007; Guzen et al., 2007). The ultrasound advantages are enhanced reaction rates, formation of purer products in high yield, easier manipulation, and it is considered as a processing aid in terms of energy conservation and waste minimization. 1,3-dipolar cycloaddition reactions are fundamental processes in organic chemistry, (Padwa, 1984) and their asymmetric version offers a powerful and reliable synthetic methodology to access five-membered heterocyclic rings in regio and stereocontrolled approach (Harwood and Vickers, 2002; Gothelf, 2002; Karlsson and Hogberg, 2001; Najera and Sansano, 2003). Criss-cross cycloaddition was described in 1917 as intermolecular reaction of benzaldazine with 2 equiv. of isothiocyanate affording a heterocyclic compound having two fused five-membered rings (Bailey and Moor, 1917). Criss-cross cycloaddition may be classified as a special type of [3 + 2] cycloaddition (Bailey and McPherson, 1917) or 1,3-dipolar cycloaddition. The formation of their products was explained in 1963 by Huisgen (Padwa, 1984) as the result of two successive 1,3-dipolar cycloadditions. Since then, a number of papers have appeared listing examples of criss-cross cycloadditions of various dipolarophiles and aldazines (Wagner-Jauregg, 1976). Many recent papers describe the synthesis of perhydrotriazolotriazoledithions by classical method, (Zachova

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et al., 2009; Verner and Potacek, 2006) but these methods have defects such as long reaction times and low yield.

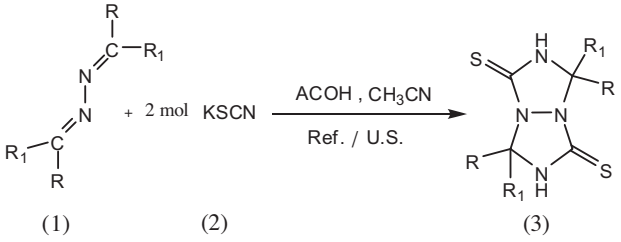
In order to expand the application of ultrasound in the synthesis of heterocyclic compounds, we wish to report a general, efficient and eco-friendly method for the synthesis of perhydrotriazolotriazoledithion derivatives. We reported aldazine as 1,3-heterodiene that has double 1,3-dipolar site and reacts with 2 equiv. of thiocyanate, in [3 + 2] cycloaddition, and give the product. Our proposed method involves features such as simplicity, fairly good efficiency, short reaction times, and excellent yields.

Meantime, it was found that these kinds of fused heterocycles possess many kinds of biological activities such as fungicidal, bactericidal, (Deshpande, 1980) analgesic, (Paget and Wikl, 1975; Kamal and Sattur, 1984) anxiolytic (Prasad et al., 1986), and anti-inflammatory (Moran et al., 1981).

2. Results and discussion

For developing novel and eco-friendly synthetic methodologies, herein we report a green, facile and efficient method for the synthesis of perhydrotriazolotriazoledithions under ultrasonic irradiation at ambient temperature. The experimental procedure for this reaction is remarkably simple and requires no toxic organic solvents. The reactions were carried out at room temperature for 10–35 min by taking a 1:2 mol ratio mixture of benzaldazine derivatives and potassium isothiocyanate, using glacial AcOH as solvent at 24 kHz under sonication (Scheme 1).

Based on the results of this study, it seems that the ultrasound irradiation improves the reaction time and yield. For more examination of the influence of ultrasound irradiation



(1) (2) (3)

R=Aryl
R_1=H, CH_3,...

Scheme 1 Preparation of perhydrotriazolotriazole derivatives.

in this transformation, comparison of the reaction by two methods, reflux conditions and ultrasound irradiation at ambient temperature was preformed (Table 1).

Using ultrasound irradiation in comparison with reflux conditions is better in both yield and especially in the reaction times. The high yield transformations were carried out without any significant amounts of undesirable byproducts. All the products were characterized by NMR, IR and elemental analyses. The presence of signal at 1227–1293 cm^{-1} in IR spectra and 10.21–11.51 ppm in ^1H NMR spectra is due to NH related to the fused five-membered rings.

3. Conclusions

This work demonstrates a novel and highly efficient methodology for the synthesis of perhydrotriazolotriazoledithions from two successive 1,3-dipolar cycloadditons of azine derivatives and potassium isothiocyanate under ultrasound irradiation. In addition to efficiency and simplicity, this protocol provides a very fast, ''green'' and low cost procedure for the synthesis of these products.

4. Experimental

Chemical substances were purchased from Merck. All of the materials were of commercial reagent grade. Melting points (°C) were determined on an ElectroMK3 apparatus using open-glass capillary and are uncorrected. IR spectra were recorded using a Perkin–Elmer FT-IR 550 spectrometer in KBr pellets and reported in cm^{-1}. NMR spectra were measured on a Bruker DRX 400 MHz spectrometer using DMSO-d_6. All chemical shift values were recorded as δ (ppm). Sonication was performed in a UP 400 S ultrasonic processor equipped with a 3 mm wide and 140 mm long probe, which was immersed directly into the reaction mixture. The operating frequency was 24 kHz and the output power was 0–400 W through manual adjustment. The elemental analyses (CHN) were obtained from a Carlo ERBA model EA 1108 analyzer or a Perkin–Elmer 240c analyzer and results agreed favorably with calculated values.

4.1. General procedure for synthesis of perhydrotriazolotriazole derivatives by reflux conditions

To a mixture of KSCN (2.5 g, 0.0257 mol), AcOH (20 ml) and CH_3CN (10 mL) was added aldazine (0.0128 mol) and was

Table 1 Synthesis of perydrotriazolotriazole derivatives by reflux conditions (Method A) and ultrasonic irradiation (Method B).

Entry	Product	R	R^1	Time (min)		Yield[a] (%)	
				Method A	Method B	Method A	Method B
1	**3a**	C_6H_5	H	105	20	91	98
2	**3b**	4-Cl C_6H_5	H	60	10	79	90
3	**3c**	3-Cl C_6H_5	H	120	16	75	87
4	**3d**	4-OMe C_6H_5	H	50	15	83	94
5	**3e**	3-Br C_6H_5	H	80	15	80	91
6	**3f**	C_6H_5	CH_3	120	30	65	80
7	**3g**	4-OH C_6H_5	CH_3	130	28	69	86
8	**3h**	3-Me C_6H_5	CH_3	180	35	68	82

[a] Yields refer to the pure isolated products.

refluxed. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting solid was washed successively with H_2O.

4.2. General procedure for synthesis of perhydrotriazolotriazole derivatives by ultrasonic irradiation

To a mixture of KSCN (2.5 g, 0.0257 mol), and AcOH (20 ml) was added aldazine (0.0128 mol) and the reaction mixture was exposed to ultrasonic irradiation at r.t. for 20 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the suspension was poured in H_2O (200 ml) and the mixture was concentrated in vacuum to remove the solvent. The resulting solid was washed successively with H_2O. After drying in vacuum the product was obtained in 80–98% yield with enough purity for spectral analysis.

*4.2.1. Tetrahydro-3,7-diphenyl-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3a**)*

Yield 98%; M.p. 187–188 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.57; UV ($CHCl_3$) λ_{max}: 244, 270 nm; FT-IR (KBr)ν_{max} (cm^{-1}): 3391, 1500, 1251; ^1H NMR (400 MHz, DMSO-d_6): δ 6.82 (2H, s, CH), 7.39 (2H, t, CH), 7.41(2H, t, CH), 7.45 (2H, t, CH), 11.42 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 73 (CH), 126.25 (CH), 127.76 (CH), 128.31 (CH), 129.73 (CH), 184.1 (C); Anal. calcd. for $C_{16}H_{14}N_4S_2$ (326.433): C 58.89, H 4.29, N 17.18, S 19.63; found: C 58.82, H 4.39, N 17.34, S 19.73%.

*4.2.2. 3,7-Bis (4-chlorophenyl)-tetrahydro-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3b**)*

Yield 90%; M.p. 200–201 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.73; UV ($CHCl_3$) λ_{max}: 244, 270 nm; FT-IR (KBr)ν_{max} (cm^{-1}): 3410, 1490, 1248; ^1H NMR (400 MHz, DMSO-d_6): δ 6.85 (2H, s, CH), 7.39 (2H, dd, CH), 7.51 (2H, dd, CH), 11.48 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 75.50 (CH), 128.4 (CH), 130.45 (CH), 133.2 (CH), 133.8 (CH), 184.1 (C); Anal. calcd. for $C_{16}H_{12}N_4S_2Cl_2$ (395.323): C 48.60, H 3.04, N 14.18, S 16.20%, Cl 17.72; found: C 48.32, H 3.13, N 14.31, S 16.29, Cl 17.81%.

*4.2.3. 3,7-Bis (3-chlorophenyl)-tetrahydro-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3c**)*

Yield 87%; M.p. 194–195 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.64; UV ($CHCl_3$) λ_{max}: 244, 269 nm; FT-IR (KBr)ν_{max} (cm^{-1}): 3415, 1500, 1252; ^1H NMR (400 MHz, DMSO-d_6): δ 6.89 (2H, s, CH), 7.16 (2H, dd, CH), 7.37 (2H, t, CH), 7.42 (2H, t, CH), 7.49 (2H, dd, CH), 11.50 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 76.62 (CH), 124.88 (CH), 126.39 (CH), 128.12 (CH), 131.84 (CH), 134.15 (C), 139.76 (C), 184.47 (C); Anal. calcd. for $C_{16}H_{12}N_4S_2Cl_2$ (395.323): C 48.60, H 3.04, N 14.18, S 16.20, Cl 17.72; found: C 48.32, H 3.13, N 14.31, S 16.29, Cl 17.81%.

*4.2.4. Tetrahydro-3,7-Bis (4-methoxyphenyl)-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3d**)*

Yield 94%; M.p. 160–161 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.67; UV ($CHCl_3$) λ_{max}: 245, 270 nm; FT-IR (KBr)ν_{max} (cm^{-1}) 3391, 1500, 1251; ^1H NMR, (400 MHz, DMSO-d_6): δ 3.81 (6H, s, CH_3), 6.76 (2H, dd, CH), 6.98 (2H, dd, CH), 7.31 (2H, dd, CH), 11.30 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.73 (CH_3), 77.03 (CH), 114.76 (CH), 127.67 (CH), 130 (C), 160.35 (C), 184 (C); Anal. calcd. for $C_{18}H_{18}N_4S_2O_2$ (386.485): C 55.96, H 4.66, N 14.51, S 16.58; found: C 55.93, H 4.76, N 14.72, S 16.68%.

*4.2.5. 3,7-Bis (3-bromophenyl)-tetrahydro-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3e**)*

Yield 91%; M.p. 158–159 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.59; UV ($CHCl_3$) λ_{max}: 243, 269 nm; FT-IR (KBr)ν_{max} (cm^{-1}): 3393, 1489, 1247; ^1H NMR (400 MHz, DMSO-d_6): δ 6.89 (2H, s, CH), 7.41 (2H, dd, CH), 7.42 (2H, t, CH), 7.56 (2H, t, CH), 7.62 (2H, dd, CH), 11.51 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.01 (CH), 125.27 (C), 127.45 (CH), 127.79 (CH), 131.22 (CH), 132.61 (CH), 136.45 (C), 184.00 (C); Anal. calcd. for $C_{16}H_{12}N_4S_2Br_2$ (482.226): C 39.85, H 2.51, N 11.62, S 13.30, Br 33.14; found: C 39.80, H 2.56, N 11.74, S 13.39, Br 33.16%.

*4.2.6. Tetrahydro-3,7-dimethyl-3,7-diphenyl-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3f**)*

Yield 80%; M.p. 118–119 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.49; UV ($CHCl_3$) λ_{max}: 242, 308 nm; FT-IR (KBr)ν_{max} (cm^{-1}): 3405, 1588, 1291; ^1H NMR (400 MHz, DMSO-d_6): δ 2.29 (6H, s, CH_3), 7.38 (2H, t, CH), 7.91 (2H, t, CH), 8.27 (2H, t, CH), 10.21 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.48 (CH_3), 70.37 (C), 127.02 (CH), 128.71 (CH), 129.68 (CH), 138.08 (C), 179.41 (C); Anal. calcd. for $C_{18}H_{18}N_4S_2$ (354.487): C 61.02, H 5.08, N 15.82, S 18.08; found: C 60.87, H 5.13, N 15.91, S 18.15%.

*4.2.7. Tetrahydro-3,7-bis(4-hydroxyphenyl)-3,7-dimethyl-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3g**)*

Yield 86%; M.p. 207–208 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.48; UV ($CHCl_3$) λ_{max}: 310 nm; FT-IR (KBr)ν_{max} (cm^{-1}): 3365, 1605, 1227; ^1H NMR (400 MHz, DMSO-d_6): δ 2.43 (6H, s, CH_3), 6.89 (2H, s, OH), 6.91 (2H, d, CH), 7.87 (2H, d, CH), 10.41 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.05 (CH_3), 89.1 (C), 115.58 (CH), 128.61 (CH),130.64 (C), 159.50 (C), 178.88 (C); Anal. calcd. for $C_{18}H_{18}N_4S_2O_2$ (386.485): C 55.94, H 4.69, N 14.50, S 16.59; found: C 55.89, H 4.78, N 14.59, S 16.67%.

*4.2.8. Tetrahydro-3,7-dimethyl-3,7-di (m-tolyl)-[1,2,4] triazolo [1,2-a] [1,2,4] triazole-1,5-dithione (**3h**)*

Yield 82%; M.p. 159–160 °C; R_f (petroleum ether:ethylacetate): 7:3 (v/v) = 0.63; UV ($CHCl_3$) λ_{max}: 314 nm; FT-IR (KBr)ν_{max} (cm^{-1}): 3386, 1587, 1293; ^1H NMR (400 MHz, DMSO-d_6): δ 2.27 (6H, s, CH_3), 2.33 (6H, s, CH_3), 7.19 (2H, dd, CH), 7.68 (2H, dd, CH), 7.76 (2H, t, CH), 7.91 (2H, t, CH), 10.18 (2H, s, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.6 (CH_3) 28.9 (CH_3), 76.2 (C), 124.01 (CH), 127.1 (CH), 128.5 (CH), 128.80 (CH), 138.2 (C), 142.4 (C), 183.5 (C); Anal. calcd. for $C_{20}H_{22}N_4S_2$ (382.540): C 62.83, H 5.67, N 14.66, S 16.75; found: C 62.77, H 5.84, N 14.81, S 16.87%.

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