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SYNTHESIS OF TRIAZOLE, THIODIAZOLE AND CURCUMIN ANALOGS VIA GREEN ROUTE

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ABSTRACT

The application of Microwave irradiation in organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology. In fact, it is one of the widely used sources of heating in organic synthesis. The basic mechanisms observed in microwave assisted syntheses are dipolar polarization and conduction. Solvent-free microwave condition has gained importance due to many advantages, like enhanced reaction rates, increased yields and improved selectivity. Further, it is simple, clean, efficient and economical for the synthesis of a large number of organic molecules. Eco – friendly reaction conditions of this technique are in tune with Green Chemistry principles. Green Chemistry aims not only for safer products, less hazardous consequences to the environment, saving energy and water, but also includes broader issues which can promote in the end sustainable development. In accordance, we synthesized successfully 4-amino-3-mercapto-5-methyl triazole (Ia) and 2-amino-5-methyl / ethyl-1-thio-3,4-diazole (IIa,IIb) by microwave irradiation method and 1,7-bis-(substituted phenyl)-1,6-heptadiene-3,5-diones (IIIa-c) under solvent free condition. The proposed methods are time efficient and produced higher yields in comparison with conventional methods of preparation.

Keywords:Green Chemistry, Microwave irradiation, Solvent free condition, Triazoles, Thiodiazoles, Curcumins.

Introduction:

With the advent of microwave technique organic synthesis has undergone anunprecedented change. Microwave brings down molecule building time to a tremendous low that classical thermal methods appear primitive. Thus, this technique rapidly gained acceptance as a valuable tool for accelerating drug discovery and development processes. The difference between microwave energy and other forms of radiation, such as X- and γ-rays, is that microwave energy is non-ionizing and therefore does not alter the molecular structure of the compounds being heated-it provides only thermal activation. The heating effect utilized in microwave assisted organic transformations is mainly due to dielectric polarization.

Green Chemistry was for many years a relatively abstract idea with no basic principles or definitions of practical applications. Now, the term Green Chemistry has been defined as "the invention, design and application of chemical products and processes to reduce or to eliminate the use and generation of hazardous substances for workers and consumers". The definition of Green Chemistry starts with the concept of invention and design. This necessitated scientists and technologists to think and formulate environmentally conducive designs and processes in which the impact of chemical reactions and chemical products is also taken into account. Hazard considerations for initial materials and final products must also be included in the performance criteria. During synthesis care must be taken to choose starting materials that can be converted into near 100% end products. This can be achieved by optimizing the conditions of synthesis. Further, the reaction should not generate any toxic by-products.The objective of Green Chemistry is to produce safer, less hazardous consequences to the environment, saving energy and water and to promote Sustainable Development. Green chemistry has gained a strong foothold in the areas of research and development in both industry and academia, especially in the industrially developed countries. Several international conferences, scientific journals, numerous publications and new courses in universities testify the increasing influence of Green Chemistry philosophy.

A relatively recent addition to organic transformations is solvent-free microwave irradiation technique. It is gaining popularity due to many advantages, like enhanced reaction rates, higher yields, improved selectivity and eco-friendly reaction conditions that are in tune with green chemistry (Lindstrom et al., 2001; Lin et al., 2004; Mistry and Desai, 2006). Along with this,methods like ultrasound, ball mill reaction, grinding etc. are also gaining attention (S. Kumar et al., 2008).Microwave assisted reactions using dry media (Pore Dinesh et al., 2012) have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of large variety of heterocyclic compounds. In the present communication an attempt has been made to synthesize 4-amino-3-mercapto-5-methyltriazole (Ia), 2-amino-5-methyl/ethyl-1-thio-3,4-diazole and 1,7-bis (substituted phenyl)-1,6-heptadiene-3,5-dione using the green route.

Materials and Methods:

Reagents such as thiosemicarbazide, acetic acid, propionic acid, acetyl acetone, 2,4-dimethoxy benzaldehyde, 2,3,4-trimethoxy benzaldehyde, 2-nitro-4-hydroxy benzaldehyde were purchased from Across Ltd. and used as it is. All the solvents used were of analytical grade and were distilled before the use.

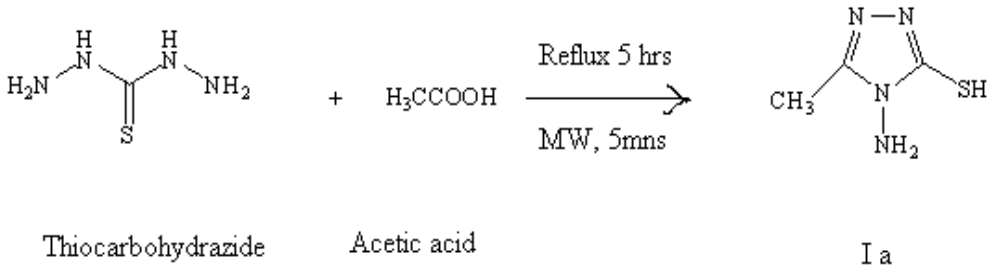
Measurements:

Melting points are uncorrected. IR spectra were recorded on Thermo Nicolet FTIR spectrophotometer at Andhra University, Visakhapatnam, and ^{1}H NMR and ^{13}C spectra were taken on JEOL Model AL 400 NMR at RRL, Bhubaneswar, in DMSO-d6 using TMS as internal reference.

Microwave irradiation was carried out using a domestic microwave oven. Elemental analysis was carried out at Micro Analytical Centre at Andhra University.

Synthesis of 4-amino-3-mercapto-5-methyl triazole (Ia):

4-amino-3-mercapto-5-methyl triazolewas synthesized by conventional method as well as microwave irradiation as outlined in 'scheme 1'. First, a mixture of thiocarbohydrazide (2.5g, 5 mmol) and glacial acetic acid (15ml) was heatedunder reflux on an oil bath for 5 hours, following the reported conventional method (Anjali Jha et al., 2010). Then the synthesis was carried out in domestic microwave oven. The time taken for this was only 5 minutes. The reaction mixture was cooled to room temperature and the excess solvent was distilled off under reduced pressure. The residual solid was crystallized from methanol resulting in the formation of shining yellow crystals. The isolated compound 4-amino-3-mercapto-5-methy triazole was characterized by various spectral methods.



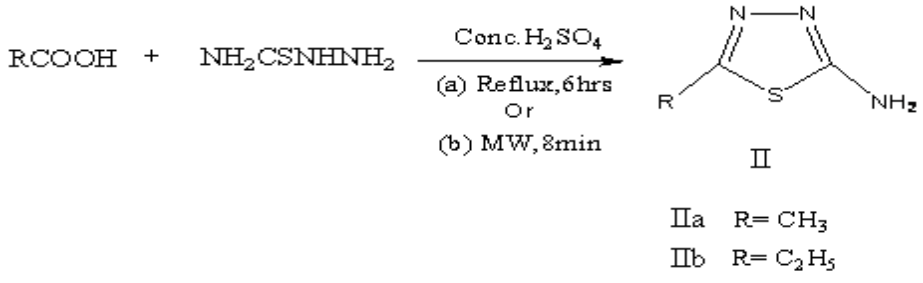
Scheme 1: Synthesis of 4-amino-3-mercapto-5-methy triazole

Characterization of 4-amino-3-mercapto-5-methyl triazole (Ia):($C_3H_6N_4S$): Yield(%): Conventional :60, Microwave: 85; mp: 203^0C;IR (υ_{max}, KBr Pellet in cm^{-1}) 3459 $cm^{-1}\upsilon$ (-NH_2), 2940 $cm^{-1}\upsilon$ (-CH_3), 1541 $cm^{-1}\upsilon$ (-C=N of the ring).NMR(DMSO-d_6 δppm) ^{1}H NMRδ12.2(SH), 7.2-7.4(NH_2), 2.2(CH_3). ^{13}C NMR169.22, 155.55, 23 ppm were assigned to (-N=C-S), (-N=C-C), (-CH_3) respectively.

Similarly a very efficient microwave-assisted protocol for the green synthesis of 2,5-disubstituted aminothiodiazole was developed. The protocol has the potential to be the most sought after method for the synthesis of drugs.

Synthesis of 2-amino-5-methyl/ethyl -1 –thio-3, 4 –diazole (IIa, IIb):

Substituted aminothiadiazoles were synthesized by conventional method as well as microwave irradiation as outlined in 'scheme 2'. First, a mixture of carboxylic acid (acetic acid, 0.6g,10mmol for the preparation of compound IIa and propionic acid, 0.74g,10mmol for the preparation of compound IIb) and thiosemicarbazide (1.092g, 12mmol) was heated in the presence of conc. H_2SO_4 (15 ml) under reflux on water bath for 6 hrs, following the reported conventional method (Pandey et al.,2003).Same ratio of carboxylic acid (acetic acid for the preparation of compound IIa and propionic acid for the preparation of compound IIb) and thiosemicarbazide in conc. H_2SO_4 (15 ml) was irradiated in microwave for 8 min. The resulting reaction mixtures obtained from both the methods were cooled to room temperature and neutralized with ammonia solution. A dark brown solid that separated out was filtered and washed repeatedly with water. It was then recrystallized from ethanol. The substituted aminothiodiazoles (IIa&IIb) were characterized by various spectral techniques.



II

IIa R= CH_3

IIb R= C_2H_5

Scheme 2 : Synthesis of 2-amino-5-methyl/ethyl thiodiazole

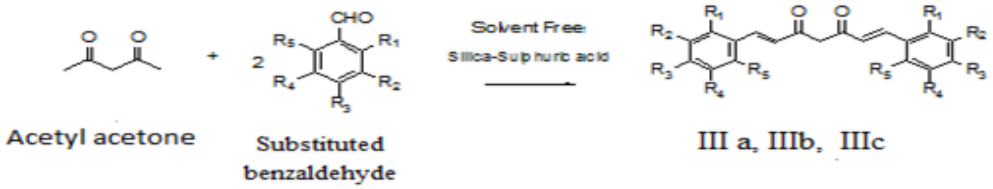
Characterization of 2-amino-5-methyl-1-thio 3,4 diazole (IIa): ($C_3H_5N_3S$): Yield(%): Conventional :50, Microwave: 70; mp: 110^0C; IR (√max, KBr pellet in cm^{-1}): 3245(NH_2); 2987, 2941 (CH_3); 2640 (CS);1555 (C=N of the ring); NMR(DMSO-d_6 δppm) ^{1}H: 6.9 (NH_2); 2.1(CH_3);^{13}C: δ 168.45 (C of thiadiazole ring attached to NH_2),δ 153.16 (C attached to CH_3); δ 20.1 (CH_3); Elemental analysis: calc. C, 31.30; H, 4.34; N, 36.52; Found: C, 31.28; H, 4.39; N, 36.60.

Characterization of 2-amino-5-ethyl-1–thio-3,4diazole (IIb): ($C_4H_7N_3S$): Yield(%): Conventional: 55, Microwave:78; mp:115^0C; IR(√max, KBr pellet in cm^{-1}):, 3240(NH_2); 2987, 2941 (CH_3); 2644 (CS); 1555 (C=N of the ring); NMR (DMSO-d_6 δ ppm) ^{1}H: 7.6 (NH_2); 3.2 (CH_2); 1.8 (CH_3); ^{13}C: δ 168.45 (C of the thiadiazole ring attached to NH_2); δ159.16(C attached to CH_2); δ 31.2 (CH_2), δ 20.1(CH_3); Elemental analysis: calc. C, 37.20; H,5.42; N, 32.55; Found: C, 37.28; H, 5.39; N, 32.58.

Simple, clean and cost effective attempts have been made to synthesize three curcumin analogs via green route in the absence of solvent. Solvent free reactions attracted many researchers due to simplicity, time efficacy and work up process. Curcumin derivatives and curcuminoids exhibit a broad spectrum of biological properties viz., anti-inflammatory, anti-oxidative stress, anti-cancer, anti-cystic fibrosis, anti HIV and controlling of Alzhemer's disease. (Mazumdar et al., 1997; Sharma et al., 2005)

Solid support mediated synthesis of 1,7-bis (substituted phenyl)-1,6-heptadiene-3,5-dione:

The solid support synthesis of substituted phenylheptadienediones was carried out using silica-sulphuric acid catalyst as outlined in 'scheme 3'. One mole of acetyl acetone, 2 moles of substituted benzaldehyde and acid catalyst were mixed and ground thoroughly. The contents were warmed with ethanol solution and cooled. The catalyst was recovered by filtration. The crude product was chromatographed to isolate pure1,7-bis-substituted phenyl-1,6-heptadiene- 3,5-diones [IIIa, IIIb, IIIc]. These yellow crystalline curcumin analogs were characterized by IR, NMR and Mass.



III a $R_1 = R_3 = OCH_3$, $R_2 = R_4 = R_5 = H$
III b $R_1 = R_2 = R_3 = OCH_3$, $R_4 = R_5 = H$
III c $R_1 = NO_2$, $R_3 = OH$, $R_2 = R_4 = R_5 = H$

Scheme 3:1,7-bis (substituted phenyl)-1,6-heptadiene-3,5-dione

Characterization of 1,7 bis(2,4-dimethoxy phenyl)1,6-heptadiene-3,5-dione (IIIa): ($C_{23}H_{25}O_6$): Yield 80%, m.p. 138°C, IR (ν_{max}, KBr, cm^{-1}) : 2900,2850,1660, 1450, 1250, 1180,1150, 1010, 987, 800, 790; ^{1}H NMR (90 MHz, $CDCl_3$, TMS) δ : 3.74 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 5.82 (s, CH_2),6.09(s,Ar-H), 6.45-6.53 (d, Ar-H), 6.74-6.93 (d, 1H, olefinic proton), 7.10-7.20 (d, Ar-H), 7,44-7.53(d,Ar-H),7.91-8.09 (d, 1H, olefinic proton); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ : 198.11, 162.20, 160.00, 137.0, 130.20, 124.20, 119.0, 105.00, 98.70, 98.19, 77.00, 75.57, 55.89, 55.04, 29.4; Mass m/e : 396, 397 (M+1),Elemental analysis: calc. C, 69.68, H, 6.16; found C, 69.60, H, 6.13. Elemental analysis: calc. C, 69.68, H, 6.16; found C, 69.60, H, 6.13.

Characterization of 1,7 bis(2,3,4-trimethoxy phenyl)1,6-heptadiene-3,5-dione (IIIb): ($C_{25}H_{29}O_8$): Yield 80%, m.p. 115°C,IR (ν_{max}, KBr, cm^{-1}) : 1650, 1290, 1212, 1160, 1034, 933, 833.^{1}HNMR (90 MHz, $CDCl_3$, TMS) δ : 3.89 (s, 6H, OCH_3), 3.90 (s, 6H, OCH_3), 3.99 (s, 6H, OCH_3), 5.83 (s, 2H, CH_2), 6.63 (d, 2H, Ar-H), 6.7 (d, 2H, Ar-H), 7.30 (d, 2H, Ar-H), 7.85 (d, 2H, olefinic proton).^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ : 199.9, 198.0, 159.1, 158.7, 156.7, 142.9, 140.6, 139.1, 127.2, 127.1, 120.7, 114.2, 107, 56.9, 55.9, 56.3, 51.9.,Mass m/e : 456.Elemental analysis : calc. C, 65.78, H, 6.18; found C, 65.70, H, 6.20.

Characterization of 1,7 bis(2-nitro,4-hydroxy phenyl)1,6-heptadiene-3,5-dione (III c): ($C_{19}H_{12}N_2O_8$): Yield 75%, m.p. 186°C, IR (ν_{max}, KBr, cm^{-1}) : 1680, 1570, 1500, 1212, 1160, 1034, 933, 830. ^{1}HNMR (90 MHz, $CDCl_3$, TMS) δ : 5.0 (s, OH), 5.83 (s, 2H, CH_2), 6.70 (d, 1H, olefinic proton), 7.07 (d, 2H, Ar-H), 7.4 (d, 2H, Ar-H), 7.61 (s, 2H, Ar-H).^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ : 198.9, 198.8, 158.6, 128.7, 122.6, 121.9, 110, 107,

51.9.,Mass m/e : 498.,Elemental analysis : calc. C, 57.29, H, 3.54, N, 7.03; found C, 57.30, H, 3.50, N, 7.00.

Results and Discussion:

Microwave assisted processes have an inherent advantage that they need no solvent, even if needed, the quantity requirement is minimal. They are generally less time consuming, more energy efficient and record higher yields. In the present work, the reactions have been conducted in the absence of solvent. The time of reaction is reduced from 5 hours to 8 minutes, which saved considerable energy and produced enhanced yield through microwave irradiation method. In case of IIIa-c synthesis, their purity is of paramount importance since these are starting material for a number of drugs like anti-inflammatory, anti-oxidative stress, anti-cancer, anti-cystic fibrosis, anti HIVetc. Adopting solid support synthesis at room temperature we have obtained 100% pure and atom economy products.

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