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# Phenacyl Bromide: An Organic Intermediate for Synthesis of Five- and Six-Membered Bioactive Heterocycles

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## Abstract

An environmentally friendly, economic synthetic protocol was advanced for synthesis of biologically and pharmacologically vital five- and six-membered heterocycles containing nitrogen, sulphur and oxygen as heteroatom. A series of thiazole derivatives was prepared by the reaction of substituted phenacyl halides and phenyl thiourea in the presence of TiO<sub>2</sub> nanoparticles (NPs) as nanocatalyst in DCM. Similarly, another series of six-membered heterocyclic compounds were synthesized by the reaction of phenacyl halides with phenylenediamine, 2-aminophenol, 2-aminobenzenethiol to produce corresponding products (1,4-quinoxaline, benzoxazine, benzothiazine) under catalytic effect of TiO<sub>2</sub> nanocatalyst. Analytical and spectral (FTIR, <sup>1</sup>H and <sup>13</sup>C NMR and SEM) techniques were employed for the structural elucidation of the synthesized compounds.

**Keywords:** environmentally friendly, thiazole derivatives, nanocatalyst, 1,4-quinoxaline, benzoxazine, benzothiazine

This chapter is divided into two sections:

1. Synthesis of five-membered heterocycles from phenacyl halides
2. Synthesis of six-membered heterocycles from phenacyl halides

## 1. Synthesis of five-membered heterocycles from phenacyl halides

### 1.1 Introduction

Cyclic compounds which contain one or more hetero atoms besides carbon are called heterocyclic compounds. Most commonly nitrogen, sulphur and oxygen are present as hetero atoms. Phosphorous, tin, boron, silicon, etc. are other less common hetero atoms. Numerous heterocyclic compounds have three to six atoms in the ring, but only those compounds which have five- or six-membered ring are by far most significant. Heterocyclic compounds are broadly circulated in nature and are

predominantly important because of the extensive variety of physiological activities related with this course of substances. Several of the important compounds contain heterocyclic rings, e.g. most of the members of alkaloids, vitamin B complex, chlorophyll, antibiotics, other plants pigments, dyes, amino acids, enzymes, the genetic material, DNA, drugs, etc. These biologically active molecules always draw the attention of chemist over the years specifically because of their biological significance.

One striking structural article characteristic to heterocycles, which continue to be exploited to great benefit by the drug industry, lies in their capability to manifest substituents around a core scaffolds in sharp three-dimensional representations [1]. In early studies of chemistry, nitrogen and sulphur containing heterocyclic compounds contained predominantly and they were thoroughly associated with the enlargement of organic chemistry which was concerned with the study of materials separated from living sources and are widely used as structural motif in drug discovery [2].

Heterocycles form by far the leading classical splits of organic chemistry and are of enormous prominence in the biological and industrial field. One of the major causes for the extensive use of heterocyclic compounds is their structures that can be precisely manipulated to attain the required alteration in function. Another important feature embraced by heterocycles is the possibility of incorporating functional groups either as substituents or as the part of ring system itself. They are also the integral part of the wide range of drugs, most of the vitamins, biomolecules, many natural products, and biologically active compounds, including antifungal, antitumor, antimicrobial [3], antibiotic, anti-inflammatory, antidepressant, antimalarial [4] antibacterial, antiviral, herbicidal, anti-HIV, antidiabetic, insecticidal and fungicidal agents. Further, most of the heterocycles possess vital applications in materials science such as dyestuff, fluorescent sensor, plastics, information storage, brightening agents, and analytical reagents. In addition, they have applications in polymer and supramolecular chemistry, especially in conjugated polymers. Moreover, they act as organic light-emitting diodes (OLEDs), organic conductors, light harvesting systems, photovoltaic cells, optical data carriers [5], chemically controllable switches, semiconductors, molecular wires, and liquid crystalline compounds. Thus consideration has been given to advanced effective new methods to synthesize heterocycles.

Now, nanotechnologies are broadly considered to have the potential to bring assistances in area as diverse as water contamination, drug development, information and communication technologies and the production of lighter and strong materials. Nanotechnologies include the conception and manipulation of materials at the nanometre scale, either by refining or reducing bulk materials or by scaling up from single groups of atoms. Nanoparticles (1–100 nm size) have a distinctive place in nanoscience and nanotechnology, not only because of their specific properties subsequent from their reduced dimensions, but also because they are auspicious building blocks for more complex nanostructures. Nanoparticles with the diameter of less than 10 nm have created extreme curiosity over the past decade due to their developed potential application in area such as nanoscale electronics, sensors, optics and catalysis. Due to this importance of nanoparticles so many efforts have been devoted to the synthesis of nanoparticles from last few years.

Furthermore, the  $\alpha$ -halogenation of ketones is an important conversion in synthetic organic chemistry [6]. Due to high reactivity of  $\alpha$ -bromoketones, they react with a large number of nucleophiles which provide a range of biologically active compounds [7].  $\alpha$ -bromoacetophenone derivatives have been examined for their active contribution in the inhibition of protein tyrosine phosphatase such as PTP1B and SHP-1 [8]. Bromination of 1,3-keto compounds at the reactive position increases bioactivity, mainly cytotoxicity against breast cancer 1A9 cells, with respect to the unsubstituted compound [9].

For several conversions employed in organic and pharmaceutical synthesis, especially,  $\alpha$ -bromo carbonyl compounds have become a significant structural motif for the development of numerous biologically active compounds for instance thiazolidin-4-one, quinoxalines [10], cyclohexanone derivatives, thiophene, pyrazolo[1,5- $\alpha$ ][1,3,5]triazine, imidazo[1,2-a][1,3,5]triazin, pyrazolines, imidazo[2,1-b] benzothiazoles [11], thiadiazine and triazolo[3,4-b][1,3,4]thiadiazine. Additionally, they are adaptable building blocks for the retro-synthesis of natural products.  $\alpha$ -bromoalkanones were prepared by direct method from  $\alpha$ -bromination of carbonyl compounds, which has fascinated significant consideration in the synthetic organic chemistry [12]. The brominated products are important intermediates for the synthesis of various useful molecules such as pharmaceuticals, surfactants, pesticides and biologically active heterocyclic compounds [13].  $\alpha$ -Bromination is also a crucial step for introducing a functional group into a molecule for further conversions.  $\alpha$ -Halogenated carbonyl compounds are broadly used in organic synthesis as appreciated reaction intermediates and they show versatile uses in organic conversions.

Thiazole ring containing heterocyclic systems are a significant structural entity for several bioactive molecules [14]. Thiazole has been used in the preparation of imperative drugs essential for antibacterial treatment, inflammation and possesses immunosuppressant activity [15]. It also possesses inhibitor's activity against antiallergies, enzyme cyclo-independent kinase, antitumor and schizophrenia [16]. Some of the thiazole derivatives prepared as fungicide as well as preventing in vivo growth of *Xanthomonas* and anti-arthritis. Amino-thiazoles act as an oestrogen receptor and as a potent class of adenosine receptor antagonists. Development of heterocyclic chemistry is still in advance phase where lot of scope is accessible for researcher. In continuation of this research, various publications on development of biologically active heterocycles containing nitrogen and sulfur as heteroatom in recent years have come into light.

Previously many synthetic methods have been used to synthesize  $\alpha$ -halo carbonyl compounds and various reagents have been applied for halogenation of active  $\alpha$ -hydrogen of carbonyl compounds such as bromine has been previously used as a elementary brominating reagent for the  $\alpha$ -bromination of carbonyl compounds but bromine is very harmful chemical to use. To overcome this limitation, several different reagents such as copper(II) bromide [17], tribromoacetophenone [18], 1,4-dioxane bromooxonium bromide [19], pyridium and tetrabutylammonium tribromide have also been employed as substitutions to bromine. The most commonly used reagents for  $\alpha$ -bromination of ketones include molecular bromine [20], N-bromosuccinimide (NBS) [21]. Recently, various methods have been reported using NBS-NH<sub>4</sub>OAc [22], NBS-photochemical [23], NBS-PTSA [24], NBS-silica supported sodium hydrogen sulphate [25], NBS-Amberlyst-15 [26], NBS-Lewis acids [27], NBS-ionic liquids [28], MgBr<sub>2</sub>-(hydroxy(tosyloxy)iodo)benzene-MW [29], N-methylpyrrolidin-2-one hydrotribromide (MPHT) [30], (CH<sub>3</sub>)<sub>3</sub>SiBr-KNO<sub>3</sub> [31], BDMS, NaBr [32].

Here we are reporting a new efficient synthetic procedure for the synthesis of  $\alpha$ -halo acetophenones and thiazole derivatives using heterogeneous catalyst TiO<sub>2</sub> NPs. Presented route is more advanced, eco-friendly and more efficient.

## 1.2 Experimental details

All the required chemicals were purchased from Sigma Aldrich, Alpha Aesar and used without further purification. The melting points were checked in open capillary tubes in melting point apparatus and are uncorrected. The completion of the reaction was checked on TLC plates coated with silica gel-G in the

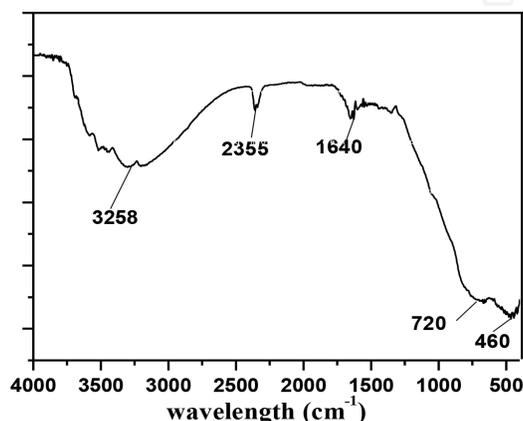
n-hexane-EtOAc ( $v/v = 7:3$ ) and visualised by exposure in UV chamber. The IR spectra were recorded on Shimadzu IR-435 spectrophotometer ( $\nu_{\max}$  in  $\text{cm}^{-1}$ ).  $^1\text{H}$  NMR, and  $^{13}\text{C}$  NMR spectra were recorded using a JEOL RESONANCE Spectrometer at 400.0 and 100.0 MHz respectively ( $\delta$  in ppm) using TMS ( $d = 0.0$ ) as an internal standard for  $^1\text{H}$  NMR, and  $\text{CDCl}_3$  was used as internal standard ( $d = 77.0$ ) for  $^{13}\text{C}$  NMR. Chemical shifts are reported in parts per million (ppm) as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). The elemental analysis (C, H and N) were performed using vario-III analyser. The nanoparticles are characterized by FTIR and SEM.

### 1.2.1 General procedure for the synthesis of $\text{TiO}_2$ NPs

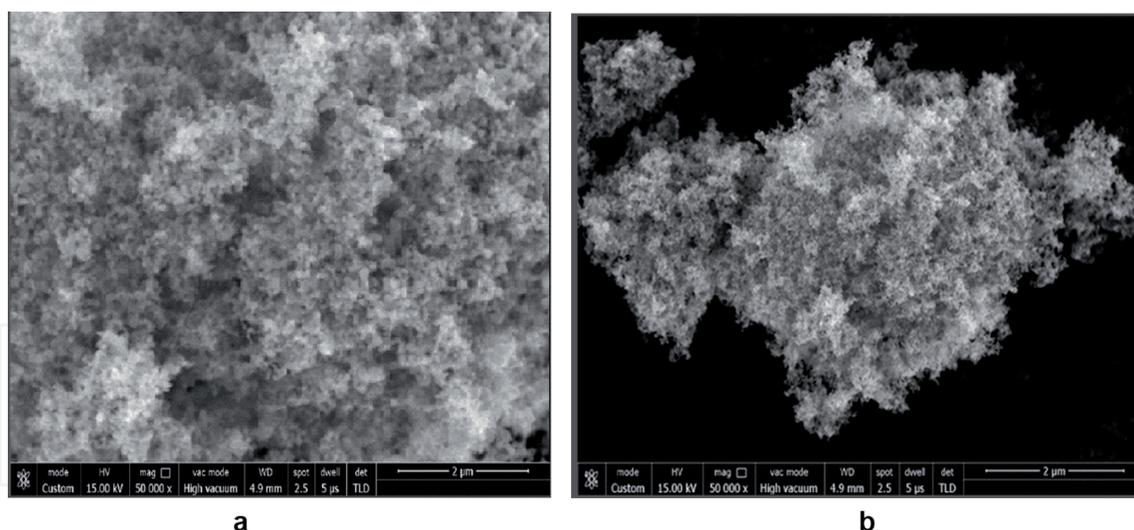
$\text{TiO}_2$  NPs were prepared by sol-gel method [33], using titanium(IV) isopropoxide. For the synthesis of  $\text{TiO}_2$  NPs,  $[\text{Ti}\{\text{OPr}^i\}_4]$  (1.75 g) was taken in round bottom flask with dry isopropanol ( $\sim 35$  ml). 2–3 drops of water-isopropanol mixture (1,1) was added to the above mentioned clear solution and magnetically stirred for 2 h then sol formation occurred immediately. To ensure complete hydrolysis, excess of water  $\sim 10$  ml {stoichiometric amount (0.22 g)}, in small lots with continuous stirring for  $\sim 4$  h was added. The mixture was again stirred for 1 h, till a gel is formed. The synthesized gel was dried in an oven ( $100^\circ\text{C}$ ) and then washed properly with acetone then an off-white powder was obtained. This powder was sintered at  $600^\circ\text{C}$  for 4 h to yield a white powder, which was characterized by FTIR and SEM as pure  $\text{TiO}_2$ .

### 1.2.2 Characterization of $\text{TiO}_2$ NPs

The  $\text{TiO}_2$  nanocatalyst was prepared using sol-gel method and characterized by various techniques using FT-IR and Scanning Electron Microscopy (SEM). The FT-IR spectrum of  $\text{TiO}_2$  NPs is given in **Figure 1**. The absorbance bands at around  $3235\text{--}3550\text{ cm}^{-1}$  were proved to the adsorbed water and hydroxyl group in nano sized  $\text{TiO}_2$  (**Figure 1**). The band observed at  $720\text{ cm}^{-1}$  is due to Ti-O-Ti while absorbance bands at  $460\text{ cm}^{-1}$  show stretching vibration due to Ti-O, which is customary with the reported IR spectra for nano  $\text{TiO}_2$  [33]. The SEM images of this oxide are revealed in **Figure 2**. The scales that are shown in **Figure 2** are of 500 nm come into sight to specify formation of agglomerates granular morphology, constituted by nano-sized crystallites.



**Figure 1.**  
The FT-IR spectra of  $\text{TiO}_2$  NPs.



**Figure 2.**  
(a and b). The SEM image of the  $\text{TiO}_2$  NPs.

### 1.2.3 General procedure for the synthesis of substituted thiazoles (3a–e)

In a 20 ml round bottom flask phenacyl bromide (**1**) (0.5 mmol) and substituted phenyl thioureas (**2**) (0.5 mmol) were added in 5 mL DCM. A catalytic amount of  $\text{TiO}_2$  NPs (5 mol%) is added to reaction mixture. Thereafter, the reaction mixture was allowed to stir at magnetic stirrer at  $50^\circ\text{C}$  for 20–30 min. The progress of reaction was monitored by TLC, the solid separated was filtered, washed with Hypo solution and recrystallized with ethanol (**Figure 3**) The detailed mechanism of the synthesis is shown in **Figure 4** (**Table 1**).

## 1.3 Spectral data of substituted thiazole (3a–e)

### 1.3.1 [4-(4-Bromo-phenyl)-thiazole-2-yl]-(4-chloro-phenyl)-amine (3a)

IR ( $\text{cm}^{-1}$ , KBr): 3315, 1611, 1462, 1370, 762, 644;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  4.03 (s, NH), 7.17 (d, 2H, Ar-H), 7.34 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 7.55 (d, 2H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.4 MHz):  $\delta$  106.2, 118.5, 119.5, 128.4, 130.5, 131.0, 131.3, 138.6, 149.4, 175.3; HRMS;  $m/z$  365.94 ( $\text{M}^+$ );  $\text{C}_{15}\text{H}_{10}\text{BrClN}_2\text{S}$ : calcd. C, 49.27; H, 2.76; N, 7.66; found C, 49.25; H, 2.75; N, 7.69.

### 1.3.2 [4-(4-Chloro-phenyl)-thiazole-2-yl]-phenyl-amine (3b)

IR ( $\text{cm}^{-1}$ , KBr): 3349, 1646, 1434, 1389, 779, 667;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  4.12 (s, NH), 7.18 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.57 (d, 2H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.4 MHz):  $\delta$  107.3, 119.3, 120.7, 130.3, 131.5, 131.9, 132.3, 140.6, 150.3, 176.9; HRMS;  $m/z$  286.03 ( $\text{M}^+$ );  $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{S}$ : calcd. C, 62.82; H, 3.87; N, 9.77; found C, 62.83; H, 3.89; N, 9.78.

### 1.3.3 [4-(4-Methoxy-phenyl)-thiazole-2-yl]-phenyl-amine (3c)

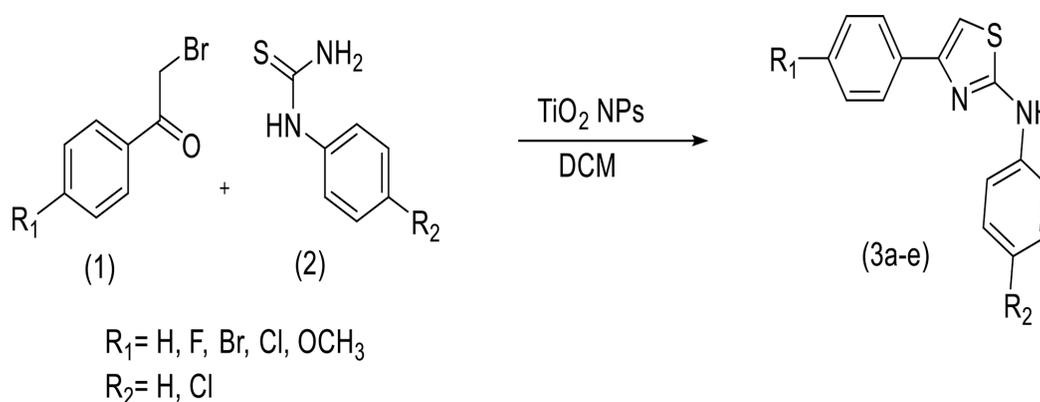
IR ( $\text{cm}^{-1}$ , KBr): 3317, 1633, 1467, 1379, 767, 648;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  4.07 (s, NH), 7.18 (d, 2H, Ar-H), 7.39 (d, 2H, Ar-H), 7.48 (d, 2H, Ar-H), 7.56 (d, 2H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.4 MHz):  $\delta$  109.5, 112.5, 120.6, 130.7, 131.8, 131.9, 132.4, 140.6, 150.7, 177.5; HRMS;  $m/z$  282.08 ( $\text{M}^+$ );  $\text{C}_{16}\text{H}_{14}\text{N}_2\text{OS}$ : calcd. C, 68.06; H, 5.00; N, 9.92; found C, 68.08; H, 5.02; N, 9.93.

## 1.3.4 [4-(4-Fluoro-phenyl)-thiazole-2-yl]-phenyl-amine (3d)

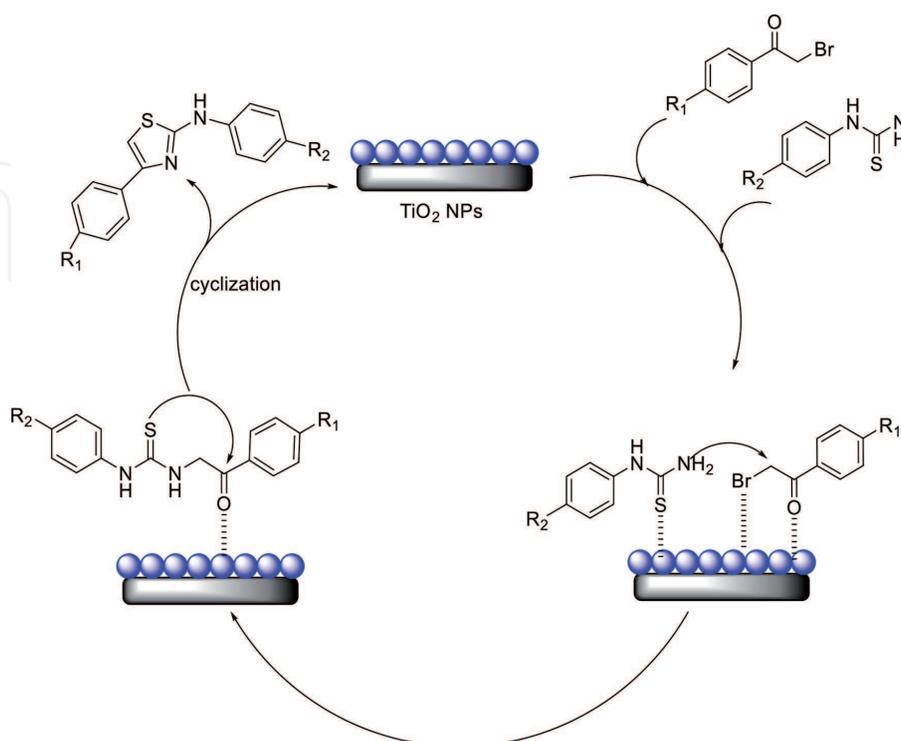
IR ( $\text{cm}^{-1}$ , KBr): 3340, 1623, 1470, 1389, 766, 665;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  4.09 (s, NH), 7.21 (d, 2H, Ar-H), 7.37 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.58 (d, 2H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.4 MHz):  $\delta$  109.8, 121.7, 123.8, 130.6, 131.6, 131.9, 132.1, 139.7, 151.5, 179.8; HRMS;  $m/z$  270.06 ( $\text{M}^+$ );  $\text{C}_{15}\text{H}_{11}\text{FN}_2\text{S}$ : calcd. C, 66.65; H, 4.10; N, 10.36; found C, 66.67; H, 4.11; N, 10.37.

## 1.3.5 [4-(2-Chloro-phenyl)-thiazole-2-yl]-phenyl-amine (3e)

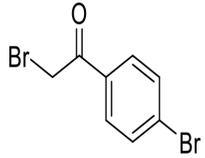
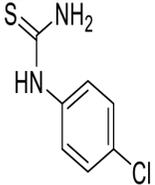
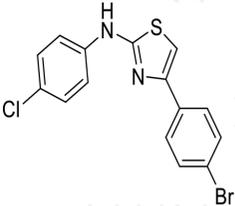
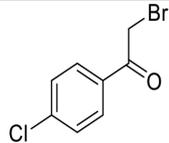
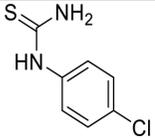
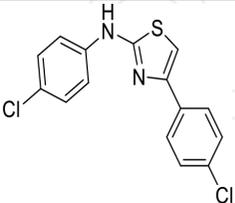
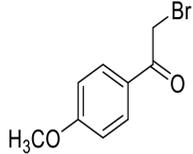
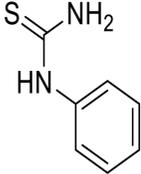
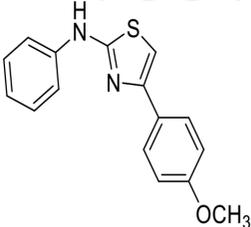
IR ( $\text{cm}^{-1}$ , KBr): 3325, 1632, 1472, 1379, 768, 647;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz):  $\delta$  4.06 (s, NH), 7.21 (d, 2H, Ar-H), 7.39 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.59 (d, 2H, Ar-H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100.4 MHz):  $\delta$  110.5, 119.5, 121.6, 131.6, 131.9, 132.2, 132.5, 141.9, 152.7, 179.3; HRMS;  $m/z$  286.03 ( $\text{M}^+$ );  $\text{C}_{15}\text{H}_{11}\text{ClN}_2\text{S}$ : calcd. C, 62.82; H, 3.87; N, 9.77; found C, 62.83; H, 3.89; N, 9.78.

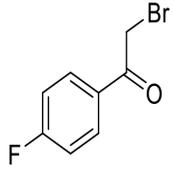
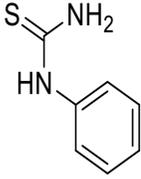
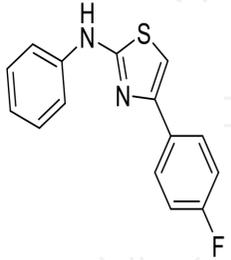
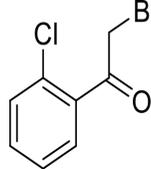
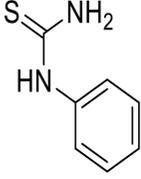
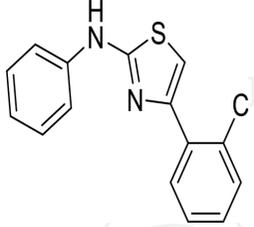


**Figure 3.**  
Synthesis of various substituted thiazole (3a-e).



**Figure 4.**  
Proposed mechanism for  $\text{TiO}_2$  NPs catalyzed thiazole synthesis.

Entry	Phenacyl bromide (1)	Phenyl thiourea (2)	Product (3a-e)	Time (min)
1			 [4-(4-Bromo-phenyl)-thiazole-2-yl]-phenyl-amine	5
2			 [4-(4-Chloro-phenyl)-thiazole-2-yl]-phenyl-amine	6
3			 [4-(4-Methoxy-phenyl)-thiazole-2-yl]-phenyl-amine	10

Entry	Phenacyl bromide (1)	Phenyl thiourea (2)	Product (3a-e)	Time (min)
4			 [4-(4-Floro-phenyl)-thiazole-2-yl]-phenyl-amine	9
5			 [4-(2-Chloro-phenyl)-thiazole-2-yl]-phenyl-amine	12

**Table 1.**  
*Synthesis of various substituted thiazole (3a-e).*

## 2. Synthesis of six-membered heterocycles from phenacyl halides: (1,4-quinoxaline, 1,4-benzoxazines, 1,4-benzothiazines)

### 2.1 Introduction

Quinoxalines are important class of nitrogen containing heterocycles, possessing nitrogen atom at 1,4 position. These heterocycles possess various pharmacological [34–38] and biological properties such as antibiotic (echinomycin, bleomycin), anticancer [39] anti-viral [40], anti-bacterial, antibiotic, and anti-inflammatory. The compounds of quinoxalines used to develop organic semiconductors [41, 42], dehydroannulenes [43], and also used in dyes [44]. Various methods have been reported in literature for the synthesis of quinoxalines, i.e. condensation of 1,2-diketone with phenylene diamine to yield the desired quinoxaline under reflux condition at ambient temperature with various solvents such as benzene, ethanol [45] with use of different catalyst like molecular iodine, copper(II) sulphate, indium(III) chloride, *o*-iodoxybenzoic acid, ceric ammonium nitrate, silica gel, gallium(III) triflate phosphorus oxychloride, oxidative coupling of epoxides with ene-1,2-diamines [46], 1,4-addition of 1,2-diamines to diazenylbutenes [47], cyclization-oxidation of phenacyl bromides with 1,2-diamines by HClO<sub>4</sub>-SiO<sub>2</sub> [48] and by using solid phase synthesis [49, 50]. Quinoxaline has also been synthesized by the chemical reaction of phenylene diamine and different substituted phenacyl bromides via solid phase [49, 50], synthesis by using different catalyst like 1,4-diazabicyclo [2,2,2]octane, trimethylsilyl chloride, perchloric acid supported on silica, KF-alumina,  $\beta$ -cyclodextrin.

1,4-Benzoxazines are important moiety of heterocyclic compounds having considerable biological [51], pharmaceutical [52] and wide range of synthetic utilities. Therefore, new methods should be developed for an efficient protocol for their synthesis. In addition of above information these compounds also served as precursors for the synthesis of many medicinally important drugs [53]. The skeleton of these type of structures are synthesized by the direct intramolecular reductive cyclization of appropriate nitroketones or by intramolecular annulation of 2-aminophenoxy ketones [54]. Benzoxazines are also prepared by the condensation reaction of 2-aminophenols with substituted phenacyl halides [55]. Although, these reported procedures are not specific and general because involvement of more than one-steps, requirement of high temperature, give low to moderate yields and use of commercially unavailable starting material. Hence the discovery of new protocols which leads to an efficient synthetic procedure for synthesis of 1,4-benzoxazine and their derivatives.

There are many reported methods in literature for the efficient synthesis for multicomponent reactions (MCRs) for the natural products, these methods are of great advantage at atom and step economy level, and these are also environmental friendly. 4*H*-1,4-benzothiazines (having nitrogen and sulphur heteroatom at 1,4 position) are a family of heterocycles possessing number of important biological and pharmacological properties [56]. A compound containing thiazine ring namely 2-benzoyl-7-chloro-3-methyl-5-trifluoromethyl-4*H*-1,4-benzothiazine [57] possessing numerous biological activities like antiemetics, neuroleptics, antihistaminics, antipsychotics, antibacterial, tranquilizers, sedatives, and anticarcinogen. This type of heterocycles has attracted considerable interest of researchers, which leads to the development of synthetic strategies. Therefore, the development and use of new MCRs have been an interesting topic in the areas of various branches of chemistry like synthetic organic, medicinal and pharmacology.

Although, these reported methods suffered from various limitations such as toxic nature of reagents, excess loading of catalyst, need of high temperature, expensive reagents and complicated work-up to complete the reaction. In present era development of green and sustainable protocols attract the attention of

scientists because the use of these above reagents causes many allergic diseases. In this connection of research, various researchers have considerable attention on use of non-hazardous reagents like nanoparticles as heterogeneous catalysts for organic transformations. So, keeping in view these facts of green technology we have tried our effort to develop, a new synthetic strategy for the synthesis of 1,4-quinoxaline, 1,4-benzoxazines, 1,4-benzothiazines catalysed by  $\text{TiO}_2$  nanoparticles (NPs).

This method is considered to be environment friendly because of use of solid heterogeneous catalyst that provides many advantages such as, ease of handling, non-corrosiveness, high yield, low cost and reusability of the used nanocatalyst.

## 2.2 General procedure for the synthesis of six-membered heterocycles

### 2.2.1 General procedure for the synthesis of 1,4-quinoxaline (3a and b)

In a 50 ml round bottom flask we took 1,2-phenylenediamine (**1**) (1 mmol) and substituted phenacyl bromide (**2**) (1 mmol) and dissolved both in dichloromethane-DCM (5 mL). Now add catalytic amount of  $\text{TiO}_2$  nanoparticles and stirring is continuous at  $50^\circ\text{C}$  for appropriate time limit. After completion of reaction, the whole content was filtered for the removal of nanocatalyst and it was well washed with ethyl acetate (10 mL). This obtained filtrate was concentrated and purified by column chromatography by using hexane/ethylacetate (15% ethyl acetate in hexane) as an eluent to yield desired quinoxaline derivatives in appropriate yields. The nanocatalyst can be recovered after thoroughly washing with ethyl acetate, air dried, and activation at  $80^\circ\text{C}$  for 3 h and can be reused for further cycles (**Figure 5**).

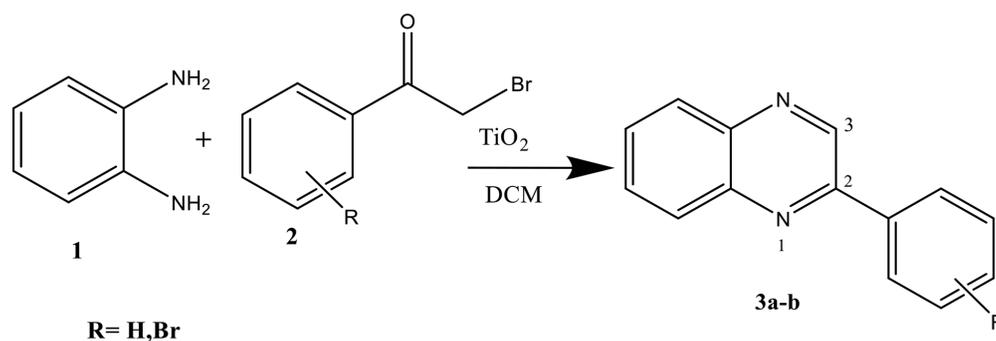
### 2.2.2 Spectral data of synthesized compounds

#### 2.2.2.1 2-Phenylquinoxaline (3a)

Dark yellow solid; M.P:  $75\text{--}78.3^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS = 0 PPM):  $\delta$  = 7.50–7.58 (m, 3H, ArH), 7.70–7.82 (m, 2H, ArH), 8.14–8.28 (m, 4H, ArH), 9.43 (s, 1H, C3-H) ppm;  $^{13}\text{C}$  NMR (100.4 MHz,  $\text{CDCl}_3$ , TMS = 0 PPM):  $\delta$  = 127.1, 129.19, 129.26, 129.5, 129.6, 130.5, 130.8, 136.4, 141.9, 142.8, 143.6, 152.8 ppm; LCMS (ESI-MS): m/z calcd. for  $\text{C}_{14}\text{H}_{10}\text{N}_2$  (M+): 206.24; found: 207.1 (M + H).

#### 2.2.2.2 2-(3-bromophenyl)quinoxaline (3b)

Light brown solid; M.P:  $132\text{--}133.8^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , TMS = 0 PPM):  $\delta$  = 7.44–7.48 (t, 1H, ArH), 7.66–7.68 (dd, 1H, ArH), 7.77–7.85 (m, 2H, ArH), 8.14–8.19 (m, 3H, ArH), 8.32–8.40 (t, 1H, ArH), 9.50 (s, 1H, C3-H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , TMS = 0 PPM):  $\delta$  = 124.4, 126.8, 129.8, 130.6, 130.9, 131.5, 131.6,



**Figure 5.**  
Synthesis of 1,4-quinoxaline.

138.9, 141.8, 142.8, 143.9, 153.2 ppm; LCMS (ESI-MS):  $m/z$  calcd. for  $C_{14}H_9BrN_2$  ( $M^+$ ): 285.14; found: 287.0 ( $M + 2H$ ).

### 2.2.3 General procedure for the synthesis of 1,4-benzoxazines (3c and d)

A catalytic amount of nanoparticles ( $TiO_2$ ) added to the stirring mixture of *o*-aminophenol (**1**) (1 mmol), substituted phenacyl bromide (**2**) (1 mmol) and triethyl amine ( $Et_3N$ ) (1.1 mmol). After the completion of the reaction the whole content was extracted with  $Et_2O$  (5X2, 10 mL). After extraction the organic layer was washed with brine (20 mL), and dried over the layer of anhydrous  $Na_2SO_4$ , concentrated and purified by column chromatography by using silica gel and  $EtOAc$ /hexane (1:20) (**Figure 6**).

#### 2.2.3.1 2-Phenyloxazine (3c)

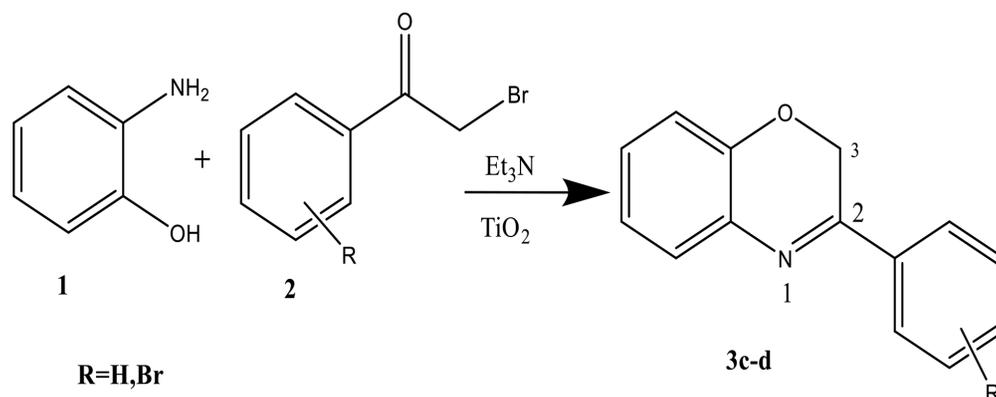
Brown solid; M.P: 88–89.5°C;  $^1H$  NMR (400 MHz,  $CDCl_3$ , TMS = 0 PPM):  $\delta$  = 7.50–7.62 (m, 3H, ArH), 7.76–7.80 (m, 2H, ArH), 8.15–8.29 (m, 4H, ArH), 4.88 (s, 2H, C3-H) ppm;  $^{13}C$  NMR (100.4 MHz,  $CDCl_3$ , TMS = 77.0 PPM):  $\delta$  = 127.5, 129.0, 129.2, 129.5, 129.6, 130.1, 130.8, 136.8, 141.5, 142.8, 143.3, 151.8 ppm; LCMS (ESI-MS):  $m/z$  calcd for  $C_{14}H_{10}N_2$  ( $M^+$ ): 206.24; found: 207.1 ( $M + H$ ).

#### 2.2.3.2 2-(3-bromophenyl) oxazine (3d)

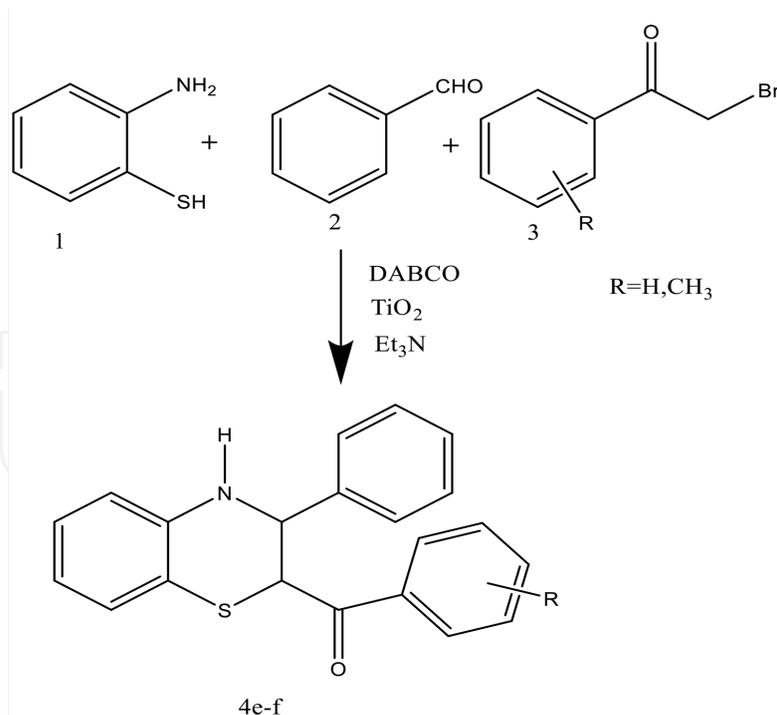
Light yellow solid, M.P: 142–143.8°C;  $^1H$  NMR (400 MHz,  $CDCl_3$ , TMS = 0 PPM):  $\delta$  = 7.51–7.58 (t, 1H, ArH), 7.66–7.70 (dd, 1H, ArH), 7.74–7.78 (m, 2H, ArH), 8.16–8.19 (m, 3H, ArH), 8.36–8.40 (t, 1H, ArH), 4.98 (s, 2H, C3-H) ppm;  $^{13}C$  NMR (100 MHz,  $CDCl_3$ , TMS = 77.0 PPM):  $\delta$  = 74.5, 126.9, 128.8, 130.8, 131.2, 131.5, 131.9, 139.9, 141.9, 142.4, 143.9, 153.2 ppm; LCMS (ESI-MS):  $m/z$  calcd for  $C_{14}H_{10}BrN_2$  ( $M^+$ ): 285.14; found: 287.0 ( $M + 2H$ ).

### 2.2.4 General procedure for the synthesis of 1,4-benzothiazines (4e and f)

In a round bottom flask the 2-aminobenzenethiol (**1**) (1 mmol), aromatic aldehyde (**2**) (1 mmol), and substituted phenacyl bromide (**3**) (1 mmol), were added in the stirring solution of the DABCO (0.2 mmol) in ( $Et_3N$ ), and stirring was continued for 6 h in an oil bath at 65°C. After the completion of the reaction the whole reaction mixture was cooled and diluted with DCM (20 mL) and then washed with water. The obtained residue was purified by column chromatography on silica gel (300–400 mesh) with  $EtOAc$  and petroleum ether (1:20, v/v) as the eluent to yield the desired product (**Figure 7**).



**Figure 6.**  
Synthesis of 1,4-benzoxazines.



**Figure 7.**  
Synthesis of 1,4-benzothiazines.

#### 2.2.4.1 Phenyl (3-phenyl-3,4-dihydro-4H-benzo[*b*][1,4]thiazin-2-yl) methanone (4e)

Light yellow solid; M.P.: 124–126°C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.86 (d,  $J = 7.5$  Hz, 2H), 7.52 (t,  $J = 7.1$  Hz, 1H), 7.41–7.26 (m, 7H), 7.08 (q,  $J = 7.5$  Hz, 2H), 6.70 (t,  $J = 8.9$  Hz, 2H), 5.12 (d,  $J = 4.8$  Hz, 1H), 4.72 (d,  $J = 5.4$  Hz, 1H), 4.45 (s, 1H) ppm;  $^{13}\text{C}$  NMR (100.4 MHz,  $\text{CDCl}_3$ )  $\delta$  47.6, 57.9, 113.8, 115.2, 118.4, 127.4, 127.8, 128.2, 128.4, 128.6, 128.6, 128.7, 133.8, 135.4, 142.4, 142.6, 194.4 ppm; HRMS (ESI) calcd for  $[\text{C}_{21}\text{H}_{17}\text{NOS} + \text{H}] + 332.1109$ , found 332.1104.

#### 2.2.4.2 (3-Phenyl-3,4-dihydro-2H-benzo[*b*][1,4]thiazin-2-yl) (*p*-tolyl) methanone (4f)

Brown solid; M.P.: 118–120°C;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.80 (d,  $J = 7.5$  Hz, 1H), 7.56 (t,  $J = 7.8$  Hz, 1H), 7.40 (t,  $J = 7.2$  Hz, 2H), 7.26 (t,  $J = 8.0$  Hz, 3H), 7.10–7.04 (m, 4H), 6.68–6.60 (m, 2H), 5.02 (d,  $J = 5.7$  Hz, 1H), 4.58 (d,  $J = 6.3$  Hz, 1H), 4.34 (s, 1H), 2.26 (s, 3H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  47.1, 57.6, 113.6, 115.0, 118.2, 127.4, 127.8, 128.2, 128.4, 128.5, 128.6, 128.7, 133.8, 135.2, 142.2, 142.6, 194.2, 21.5 ppm; HRMS (ESI) calcd. for  $[\text{C}_{22}\text{H}_{19}\text{NOS} + \text{H}] + 346.1266$ , found 346.1260.

### 3. Results and discussion

In this chapter we have tried to develop an efficient protocol for the synthesis of five-membered disubstituted derivatives (**thiazole**, **3a–e**, **Figure 3**) by using  $\text{TiO}_2$  NPs in moderate to excellent yields from the starting materials phenacyl halides and thioureas. Similarly, six-membered nitrogen containing heterocycles (**quinoxaline derivatives**, **3a, b**, **Figure 5**) from *o*-phenylenediamines and substituted phenacyl bromides in the presence of  $\text{TiO}_2/\text{DCM}$  at 50°C. In the similar way, six-membered nitrogen and oxygen containing heterocycles (**benzoxzines**, **3c** and **d**, **Figure 6**) was

synthesized under the set of conditions  $\text{Et}_3\text{N}/\text{TiO}_2$  at room temperature by annulation of o-aminophenols with substituted phenacyl bromides via one pot process. 1,4-benzothiazines are prepared by the reaction of the benzaldehyde, phenacyl halides and 2-aminothiophenols in the presence of set of conditions DABCO,  $\text{TiO}_2$ ,  $\text{Et}_3\text{N}$  to yield benzothiazine (**4e** and **f**, **Figure 7**). The  $\text{TiO}_2$  NPs was characterised by FTIR and SEM images which confirmed the synthesis of  $\text{TiO}_2$  NPs in the nano range.

#### 4. Conclusion

In conclusion, we have developed a green and economic procedure for the synthesis of bioactive five- and six-membered heterocycles. This synthetic methodology allowed us to synthesize products in good to excellent yields, which is irrespective to the functional groups which are present in the starting material. The used protocol is mild and environmental friendly. There are many merits of the used protocol like, low cost of green catalyst, obtaining high yield of products, operational simplicity, and the catalyst can be reused without any significant loss in catalytic property up to four catalytic cycle. These outstanding features of this method make it environmentally friendliness.

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