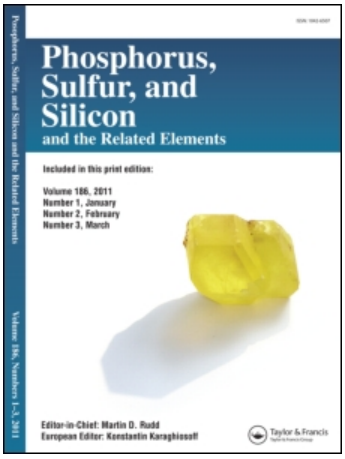


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

The Utility of 2-(5,6,7,8-Tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidin-4-yloxy) Acethydrazide in Heterocyclic Synthesis

M. E. Azab[a]; M. A. E. Ibraheem[a]; H. M. F. Madkour[a]
[a] Synthetic Organic Chemistry Laboratory, Chemistry Department, Ain Shams University, Abbassiya, Cairo, Egypt

To cite this Article Azab, M. E. , Ibraheem, M. A. E. and Madkour, H. M. F.(2006) 'The Utility of 2-(5,6,7,8-Tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidin-4-yloxy) Acethydrazide in Heterocyclic Synthesis', Phosphorus, Sulfur, and Silicon and the Related Elements, 181: 6, 1299 — 1313
To link to this Article: DOI: 10.1080/10426500500326834
URL: http://dx.doi.org/10.1080/10426500500326834

Phosphorus, Sulfur, and Silicon, 181:1299–1313, 2006

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500500326834

Taylor & Francis
Taylor & Francis Group

The Utility of 2-(5,6,7,8-Tetrahydrobenzo[*b*]thieno-[2,3-*d*]pyrimidin-4-yloxy) Acethydrazide in Heterocyclic Synthesis

M. E. Azab
M. A. E. Ibraheem
H. M. F. Madkour
Synthetic Organic Chemistry Laboratory, Chemistry Department, Ain Shams University, Abbassiya, Cairo, Egypt

*Because of being a versatile synthon, the title compound **2** was utilized to construct different heterocyclic systems including pyrazol-4-carbonitrile **3**, pyrazolone **4**, triazole-5(4H)-thione **7**, aminotriazole **9**, oxadiazoles **10** and **12**, thiazolidine **13**, and oxatriazole **14**. All new synthesized compounds were structurally confirmed by elemental analyses and spectroscopic data.*

Keywords Acethydrazide; oxadiazole; oxatriazole; pyrazolone; thiazole; triazole

INTRODUCTION

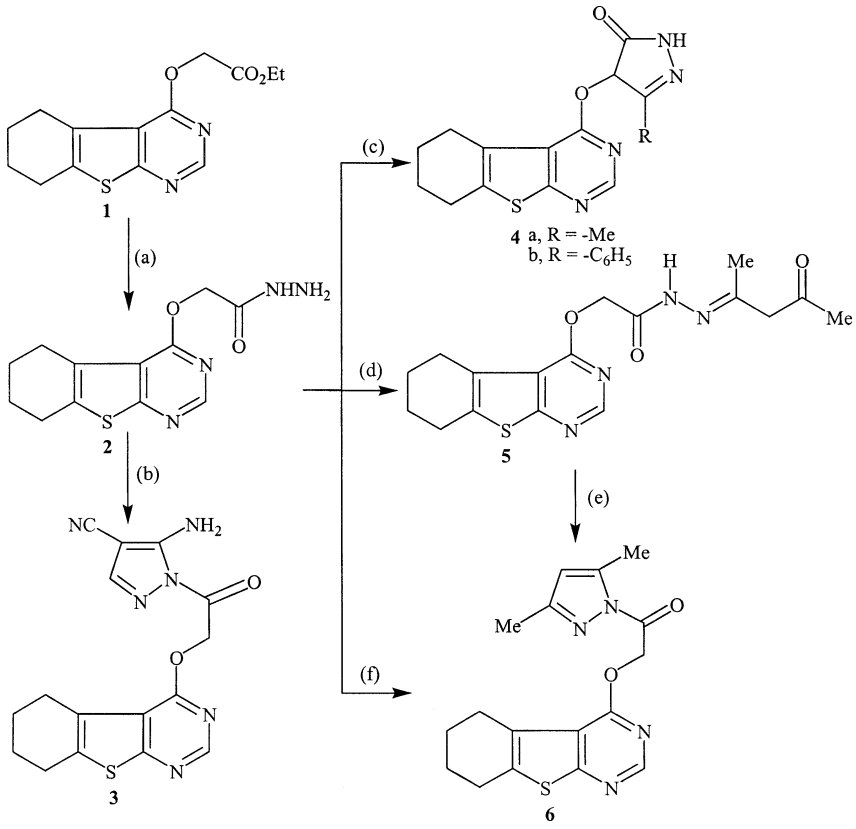
Thieno[2,3-d]pyrimidines are well known in the literature for their biological activity and diversity of applications. For example, these compounds are used in medicine as antibiotics,[1] and antiulcer,[2] antiallergic,[3] antihypertensive,[4] bactericidal,[5] blood, and platelet aggregation inhibitory agents.[6] In other fields, they are used as herbicides[7] and insecticides.[8]

For the growing worldwide interest in the synthesis of new thieno[2,3-d]-pyrimidine derivatives and in continuation of our research program aiming to the synthesis of new heterocyclic compounds of potentail biological activities,[9–17] we report herein the synthesis of some new thieno[2,3-d]pyrimidines attached to five-membered heterocyclic systems using 2-(5,6,7,8-tetrahydrobenzo[b]thieno[2,3-d]-pyrimidin-4-yloxy)acethydrazide (**2**) as a versatile starting material.

Received March 29, 2005; accepted June 21, 2005.
Address correspondence to H. M. F. Madkour, Ain Shams University, Chemistry Department, Faculty of Science, Cairo, Egypt. E-mail: nfmakour@yahoo.com

RESULTS AND DISCUSSION

Compound **2** was prepared by condensation of the corresponding ethyl ester **1** with hydrazine hydrate in refluxing ethanol (Scheme 1). Compound **2** gave compatible elemental analysis and IR and ^{1}H-NMR spectroscopic data.



SCHEME 1 (a) $N_2H_4 \cdot H_2O$, (b) EtO-CH=C(CN)$_2$, (c) RCOCl, (d) Ac_2CH_2/AcOH, (e) Ac_2O/Δ, and (f) Ac_2 CH_2/EtOH.

The hydrazide group in the versatile synthon **2** could be utilized to build up several five-membered rings attached to position-4 of the benzothienopyrimidine moiety. Thus, the pyrazole ring was obtained by reacting compound **2** with ethoxymethylenemalononitrile in refluxing ethanol[18] to afford the pyrazole derivative **3** (Scheme 1).

Another reaction that led to the formation of a pyrazole ring was carried out by heating compound **2** with acetyl and/or benzoyl chloride

in refluxing pyridine to produce the pyrazolone derivatives **4a** and **4b**, respectively.

The pyrazole **6** was also obtained when compound **2** was allowed to react with 2,4-pentanedione in refluxing dry ethanol.[19] On the other hand, compound **6** could be prepared in a two-step process. Thus, hydrazide **2** reacted with 2,4-pentanedione in refluxing acetic acid[19] to yield the acyclic monohydrazone **5**, which was then cyclized to **6** by heating under reflux with freshly distilled acetic anhydride (Scheme 1). The IR spectrum of **5** showed, besides the expected absorption bands due to NH, aliphatic and aromatic stretching CH groups, two strong absorption bands at 1724 and 1665 cm^{-1} corresponding to ketonic C=O and acyclic amide C=O, respectively. That of **6**, on the other hand, showed only one absorption band in the carbonyl region at 1675 cm^{-1} attributed to the amidic C=O, among other expected absorption bands suitable for the assigned cyclized structure. The ^{1}H-NMR spectra of **5** and **6** agreed with the structures.

The hydrazide **2** could also be used as a precursor for the synthesis of 1,2,4-triazoles. Thus, when compound **2** was allowed to react with phenyl isothiocyanate[20,21] in refluxing dry pyridine, the triazole-5(4H)-thione derivative **7** was isolated (Scheme 2).

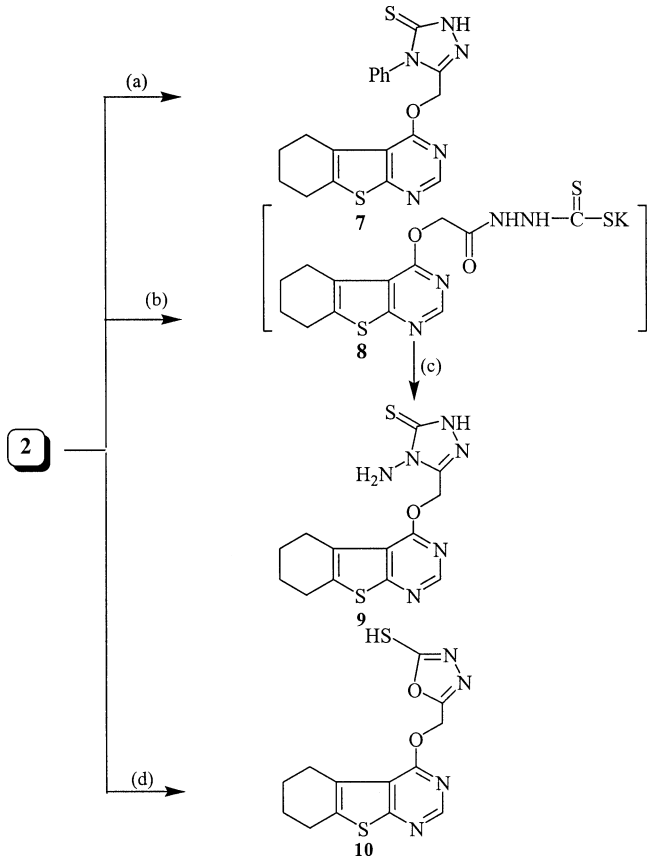
When the hydrazide **2** reacted with carbon disulfide at r.t. in the presence of potassium hydroxide[22,23] followed by stirring the produced potassium salt **8** with hydrazine hydrate in situ at r.t., the product was identified as the triazol **9** (Scheme 2).

Another new heterocyclic system was obtained when reaction conditions of the reaction of carbon disulfide with the hydrazide **2** were altered. Thus, when hydrazide **2** was heated under reflux with carbon disulfide in alcoholic potassium hydroxide solution, 1,3,4-oxadiazole derivative **10** was obtained (Scheme 2).

The condensation of **2** with selected aromatic aldehydes, namely benzaldehyde, 4-chloro-benzaldehyde and/or salicylaldehyde in ethanol,[21,24] in the presence of a catalytic amount of piperidine furnished the benzylidene hydrazide derivatives **11a–c**, respectively (Scheme 3). The ^{1}H-NMR spectrum of **11c** revealed its presence in an (*E*)- and (*Z*)-isomer mixture (Scheme 4).

In the ^{1}H-NMR spectrum of **11c** (DMSO-d_6), the protons of –N=CH, –CONH–, –O–CH_2–CO–, and phenolic –OH appear twice due to the presence of both isomers. In the *E*-isomer, these protons are generally more deshielded due to H-bonding and a lack of steric hindrance that leads to planarity and consequently to a stronger mesomeric effect.

Stirring the hydrazones **11a** and/or **11b** with bromine[24] in acetic acid containing anhydrous sodium acetate at r.t. afforded the oxadiazole derivatives **12a**,**b**. An alternative route to obtain oxadiazoles



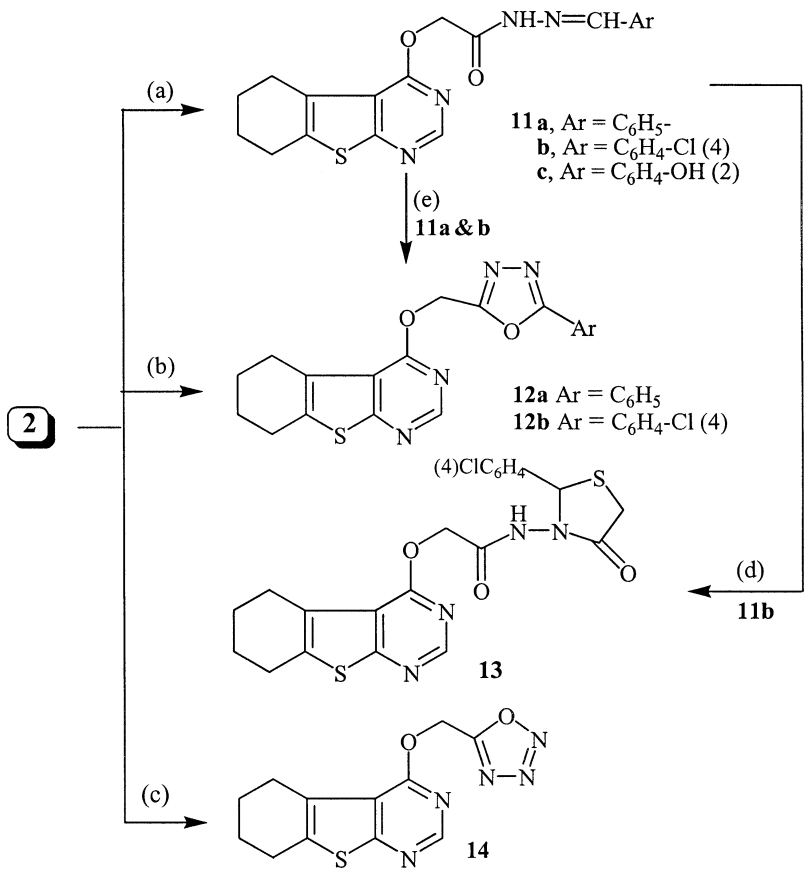
SCHEME 2 (a) PhNCS, (b) CS_2/KOH/rt, (c) N_2H_4/rt, and (d) CS_2/alc·KOH/Δ.

12a,**b** consists in heating the hydrazide **2** with benzoic acid and/or 4-chlorobenzoic acid in phosphorus oxychloride[25] (Scheme 3).

On the other hand, when the hydrazone **11a** was heated under reflux with thioglycollic acid in dry benzene, the addition of the nucleophilic sulphur atom to the C=N bond took place, followed by cyclization to furnish the thiazole derivative **13** (Scheme 3).

The oxatriazole derivative **14** was obtained with good yield via the treatment of the hydrazide **2** with nitrous acid[26] (Scheme 3). The IR spectrum of oxatriazole **14** showed that the compound is most probably present as two isomers in dynamic equilibrium as in Scheme 5.

The presence of the enimine form was confirmed by the appearance of absorption bands at 3373 and 1669 cm^{-1} corresponding to NH and C=N groups, respectively.

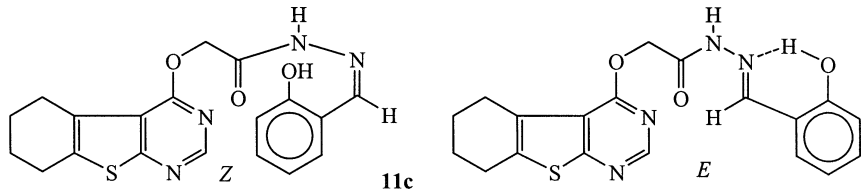


SCHEME 3 (a) ArCH, (b) ArCOOH/$POCl_3$, (c) $NaNO_2$/AcOH, (d) HS-CH_2-COOH, and (e) Br_2/AcOH.

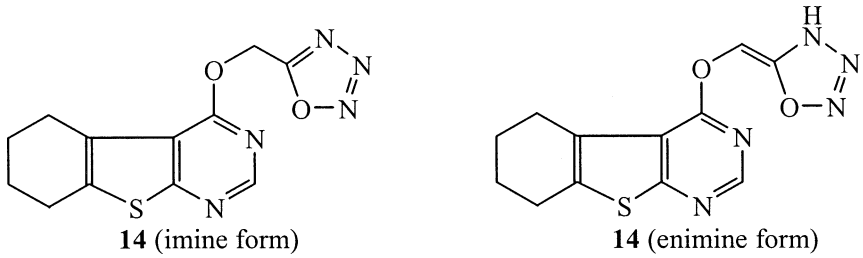
Moreover, attempts were made to cyclize the hydrazide moiety of **2** using ethyl orthoformate or formic acid to obtain 1,3,4-oxadiazoles[26] and ethyl acetoacetate to obtain a pyrazolone.[27] However, these attempts failed to produce the desired ring systems. Instead, the products were the N′-ethoxymethylene derivative **15**, the benzothienopyrimidinyl-oxyacetic acid derivative **16**, and the hydrazonobutanoate derivative **17**, respectively. Alkaline hydrolysis of the butanoate ester **17** afforded the acetic acid derivative **16** (Scheme 6).

EXPERIMENTAL

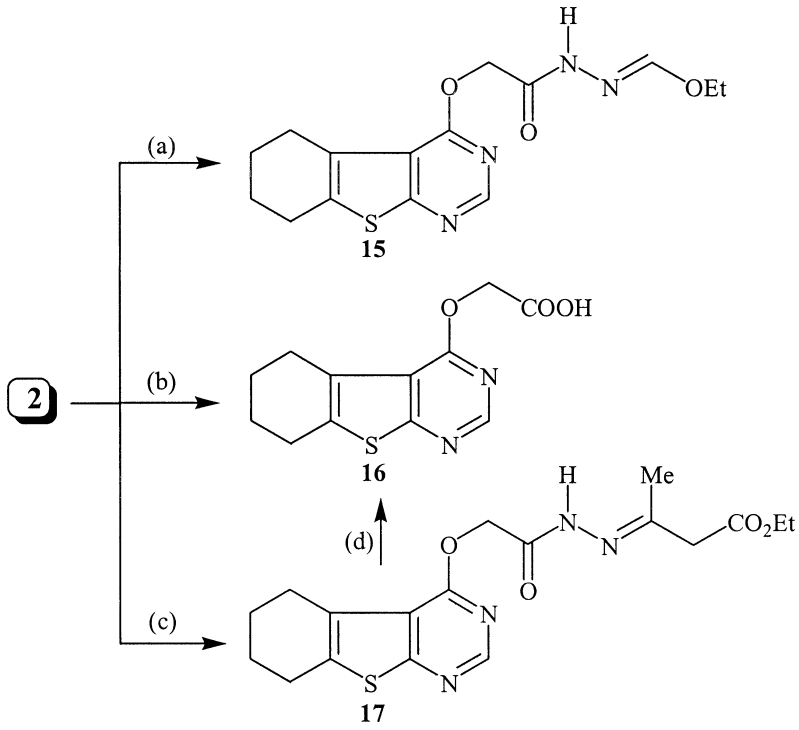
All melting points reported are uncorrected. The IR spectra were measured on a Unicam (200 Spectrometer) or Mattson infinity series FT-IR



SCHEME 4



SCHEME 5



SCHEME 6 (a) $HC(OEt)_3$, (b) HCOOH, (c) $MeCOCH_2CO_2Et$, and (d) aq. NaOH/Δ.

using KBr wafer technique. The ^{1}H-NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on a Varian Gemini 200 MHz instrument using TMS as an internal standard. Mass spectra were recorded on Shimadzu GC-MS-QP 1000 EX instrument operating at 70 eV. TLC was preformed on ready-to-use silica gel plates Merck 60 to moniterate reactions and test the purity of the new synthesized compounds.

Ethyl (5,6,7,8-Tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-Yloxy)acetate (1)

An equimolar mixture of 4,5,6,7-tetrahydrobenzo[b]thieno[2,3-d]pyrimidin-4(3H)-one[28,29] (30 mmol; 6.18 g), ethyl chloroacetate (30 mmol; 3 mL) and excess K_2CO_3 (8 g) in 100 mL of dry acetone was refluxed on a water bath for 24 h. Most of the solvent was evaporated, and the reaction mixture was then poured onto ice water to give a solid product. Crystallization of the crude product from light petroleum (60–80°C) yielded the title product **1** as white crystals; m.p: 102–105°C; yield: 64%. IR: ν 3046 (CH_{ar}), 2933 (CH_{al}), 1739 (C=O), 1677 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) : δ 1.30 (t, 3H, $OCH_2\underline{CH_3}$, J = 4.4 Hz), 1.85 (m, 4H, C-6H and C-7H), 2.79 (br.s, 2H, C-5H), 2.98 (br.s, 2H, C-8H), 4.26 (q, 2H, $OC\underline{H_2}CH_3$, J = 4.8 Hz), 4.67 (s, 2H, O-CH_2-CO), 7.85 (s, 1H, C-2H); anal. calcd. for $C_{14}H_{16}N_2O_3S$ (292): C, 57.53; H, 5.52; N, 9.48; found: C, 57.44; H, 5.41; N, 9.39.

2-(5,6,7,8-Tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-Yloxy)-acetohydrazide (2)

A mixture of **1** (10 mmol; 2.92 g) and hydrazine hydrate (10 mmol; 0.5 ml) in ethanol (60 mL) was heated under reflux for 2 h, left to cool, filtered off, dried, and then recrystallized from ethanol to afford **2** as white crystals; m.p: 253–255°C; yield: 61.14%. IR: ν 3321 and 3277 (NH_2 and NH), 3036 (CH_{ar}), 2930 (CH_{al}), 1663 (C=O acyclic amide) 1622 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6) : δ 1.78 (m, 4H, C-6H and C-7H), 2.74 (dxd, 2H, C-5H), 2.85 (dxd, 2H, C-8H), 4.30 (s, 2H, NH_2), 4.56 (s, 2H, OCH_2CO), 8.24 (s, 1H, C-2H), 9.40 (s, 1H, CONH); anal. calcd. for $C_{12}H_{14}N_4O_2S$ (278): C, 51.80; H, 5.04; N, 20.14; found: C, 51.61; H, 4.97; N, 19.97.

5-Amino-1-[(5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-Yloxy)acetyl]-1-H-pyrazole-4-carbonitrile (3)

To a solution of hydrazide **2** (10 mmol; 2.78 g) in 50 mL of ethanol, ethoxy-methylene malononitrile (10 mmol; 1.22 g) was added, and

the reaction mixture was heated under reflux for 10 h and left to cool. The solid product that deposited was collected by filtration, washed, dried, and recrystallized from benzene to give **3** as yellow crystals; m.p: over 300°C; yield: 55.33%. IR: ν 3323 and 3277 (NH_2), 3055 (CH_{ar}), 2934 (CH_{al}), 2217 (C≡N), 1666 (C=O), 1625 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6) : δ 1.77 (m, 4H, C-6 and C-7H), 2.75 (br.s, 2H, C-5H), 2.85 (br.s, 2H, C-8H of tetrahydrobenzothienopyrimidine), 4.30 (br.s, 2H, NH_2), 4.56 (s, 2H, O-CH_2CO), 8.24 (s, 1H, pyrimidine moiety), 9.38 (s, 1H, pyrazole moiety); anal. calcd. for $C_{16}H_{14}N_6O_2S$ (354): C, 54.23; H, 3.89; N, 23.71; found: C, 53.89; H, 3.64; N, 23.54.

4-[3-Methyl-1H-5(4H)-pyrazolon-4-Yl]-oxy-5,6,7,8-tetrahydro[b]benzothieno[2,3-d]-pyrimidine (4a)

To a solution of acetohydrazide **2** (10 mmol; 2.78 g) in 5 mL of pyridine, acetyl chloride (5 mL) was added, and the reaction mixture was stirred for 1 h and acidified with cold diluted HCl. The precipitated solid product was filtered off, dried, and then recrystallized from light petroleum (40–60°C) to give **4a** as white solid; m.p: 162–164°C; yield: 58.2%. IR: ν 3480 (OH), 3250 (NH), 3050 (CH_{ar}), 2940 (CH_{al}), 1732 (C=O), 1673 cm^{-1} (C=N); anal. calcd. for $C_{14}H_{14}N_4O_2S$ (302): C, 55.63; H, 4.67; N, 18.53; found: C, 55.42; H, 4.35; N, 18.34.

4-[3-Phenyl-1H-5(4H)pyrazolon-4-Yl]oxy-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]-pyrimidine (4b)

To a solution of acetohydrazide **2** (5 mmol; 1.39 g) in 5 mL of pyridine benzoyl chloride (5 mL) was added, and the reaction mixture heated under reflux on a water bath for 10 h, left to cool, and acidified with cold diluted HCl. The solid product that separated out was filtered off. Crystallization of the crude product from benzene yielded compound **4b** as white crystals; m.p: 148–151°C; yield: 60.7%. IR: ν 3455 (OH), and 3200 (NH), and 3018 (CH_{ar}), and 2939 (CH_{al}), 1736 (C=O),1672 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6) : δ 1.80 (br.s, 4H, C-6 and C-7H), 2.77 (br.s, 2H, C-5H), 2.88 (br.s, 2H, C-8H), 4.77 (s, 1H, CH of pyrazole moiety), 5.18 (s, 1H, OH of lactim form), 8.46–6.88 (m, 6H, 5ArH and C-2H), 11.75 (br.s, 1H, NH); anal. calcd. for $C_{19}H_{16}N_4O_2S$ (364): C, 62.63; H, 4.40; N, 15.38; found: C, 62.43; H, 4.15; N, 15.14.

2-{[(5,6,7,8-Tetrahydro[b]benzo-thieno[2,3-d]pyrimidin-4-yloxy)acetyl]hydrazono}pentan-2,4-dione (5) and 4-[2-(3,5-dimethyl-1H-pyrazol-1-Yl)-2-oxoeth Oxy]-5,6,7,8-tetrahydro-[1]benzothieno-[2,3-d]-pyrimidine (6)

(1) In Acetic Acid

An equimolar mixture of hydrazide **2** (10 mmol; 2.78 g) and acetylacetone (10 mmol; 1 mL) in 30 mL of glacial acetic acid was refluxed for 6 h. Most of the solvent was evaporated, and the reaction mixture was left to cool; the solid product that separated out was filtered off. Crystallization of the crude product from ethanol yielded **5** as pale yellow crystals; m.p: 278–280°C; yield: 48.5%. IR: ν 3393 (OH), 3228 (NH), 3049 (CH_{ar}), 2937 (CH_{al}), 1724 (C=O ketone) 1665 cm^{-1}(C=O acyclic amide); ^{1}H-NMR (DMSO-d_6) : δ 1.77 (br.s, 4H, C-6 and C-7H of tetrahydrothienopyrimidine residue), 1.81 (s, 3H, N=C-CH_3), 1.85 (s, 2H, N=C–CH_2–), 2.75 (br.s, 2H, C-5H), 2.84 (br s, 2H, C-8H), 4.69 (s, 2H, –OCH_2–CO), 8.28 (s, 1H, C-2H) and 9.97 and 10.28 (two s, 1H, lactam-lactim dynamic mixture, NH-C=O $\rightleftharpoons$ N=C-OH); anal. calcd. for $C_{17}H_{20}N_4O_3S$ (360): C, 56.67; H,5.56; N, 15.56; found: C, 56.86; H, 5.69; N, 15.74.

(2) In Ethanol

Acetylacetone (10 mmol; 1 mL) was added to the hydrazide **2** (10 mmol; 2.78 g) in 50 mL of absolute ethanol and refluxed for 10 h. Most of the solvent was evaporated, and the reaction mixture was left to cool; the solid product that deposited was filtered off. Crystallization from ethanol gave **6** as white crystals; m.p: 222–225°C; yield: 50.58%. IR: ν 3226 (enolic OH), 3083 and 3019 (CH_{ar}), 2942 (CH_{al}), 1675 (C=O) and 1660 cm^{-1}(C=N); ^{1}H-NMR (DMSO-d_6) : δ 1.76 (br.s, 7H, C-6 and C-7H of thienopyrimidine nucleus and CH_3 at C-5 of pyrazole nucleus), 2.03 (s, 3H, CH_3 at C-3 of pyrazole), 2.76 (br.s, 2H, C-5H of thienopyrimidine), 2.87 (br.s, 2H, C-8H of thieno-pyrimidine), 3.31 (s, 1H, enolic OH), 4.99 (s, 2H, OCH_2CO), 6.45 (s, 1H, C<u>H</u>=C-OH), 6.53 (s, 1H, C-4 of pyrazole) and 8.24 (s, 1H, C-2H thienopyrimidine); anal. calcd. for $C_{17}H_{18}N_4O_2S$ (342): C, 59.65; H, 5.26; N, 16.37; found: C, 59.56; H, 5.17; N, 16.25.

Converting Compound 5 Into 6

Compound **5** (5 mmol; 1.8 g) was refluxed in acetic anhydride for 6 h. The reaction mixture was poured into ice water with vigorus stirring; the solid product that deposited was filtered off and recrystalled from ethanol to give **6**.

3-[(5,6,7,8-Tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-Yloxy)methyl]-4-Phenyl-1,2,4-Triazole-5(4H)-thione (7)

A mixture of hydrazide **2** (10 mmol; 2.78 g) and phenylisothiocyanate (10 mmol; 0.5 mL) in pyridine (20 mL) was heated under reflux for 12 h. Most of the solvent was evaporated, left to cool, and acidified with cold diluted HCl. The solid product that separated out was filtered off, dried, and then recrystallised from benzene to give **7** as white solid; m.p: 188–190°C; yield: 36.8%. IR: ν 3232 (NH), 3053 (CH_{ar}), 2933 (CH_{al}), 1663 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$) : δ 1.84 (br.s, 4H, C-6 and C-7H of tetrahydrobenzothienopyrimidine nucleus), 2.73 (br.s, 2H, C-5H), 2.95 (br.s, 2H, C-8H), 4.65 and 7.86 (two s exchangeable, NH-C=S $\rightleftharpoons$ N=C-SH), 4.97 (s, 2H, OCH_2-), 7.26–7.52 (m, 5H, ArH) and 8.10 (s, 1H, C-2H of tetrahydrobenzothieno-pyrimidine nucleus); anal. calcd. for $C_{19}H_{17}N_5OS_2$ (395): C, 57.72; H, 4.30; N, 17.72; found: C, 57.59; H, 4.21; N, 17.68.

4-[(4-Amino-5-thioxo-1,2,4-triazol-3-yl)methoxy]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]-pyrimidine (9)

A mixture of hydrazide **2** (10 mmol; 2.78 g), CS_2 (3 mL), and ethanolic KOH solution (10%; 40 mL) was stirred at r.t. for 3 h. The solid product **8** that separated out was filtered off and disolved in water (20 mL); hydrazine hydrate (100%; 3 mL) was added, and the reaction mixture was stirred at r.t. for 24 h and acidified with cold diluted HCl. The solid product that precipitated down was filtered off by suction, washed with cold water, dried, and then recrystallized from ethanol to afford **9** as white crystals; m.p: 280–282°C; yield: 82.3%. IR: ν 3324 and 3277 (NH_2), 3030 (CH_{ar}), 2933 (CH_{al}), 1664 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6) : δ 1.79 (br s, 4H, C-6 and C-7H), 2.25 (s, 2H, NH_2), 2.77 (br.s, 2H, C-5H), 2.86 (br.s, 2H, C-8H), 5.21 (s, 2H, O-CH_2-C=), 7.18 (s, 1H, NH), 8.27 (s, 1H, C-2H), anal. calcd. for $C_{13}H_{14}N_6OS_2$ (334): C, 46.71; H, 4.19; N, 25.15; found: C, 46.59; H, 4.01; N, 24.97.

4[(5-Mercapto-1,3,4-oxadiazol-2-yl)methoxy]-5,6,7,8-tetrahydro[1]benzothieno[2,3-D]pyrimidine (10)

An equimolar mixture of hydrazide **2** (10 mmol; 2.78 g) and CS_2 (10 mmol; 0.9 mL) in 50 mL of ethanol was refluxed for 8 h. Most of the solvent was evaporated, and the reaction mixture was left to cool to give a solid product. Crystallization of the crude product from ethanol yielded the title product **10** as pale yellow crystals; m.p: 236–238°C; yield: 31.25%. IR: ν 3088 (CH_{ar}), 2935 (CH_{al}), 1657 cm^{-1} (C=N);

^{1}H-NMR (DMSO-d_6) : δ 1.79 (br s, 4H, C-6 and C-7H), 2.51 (br.s, 2H, C-5H), 2.80 (br.s, 2H, C-8H), 4.72 (s, 1H, SH), 5.32 (s, 2H, O-CH_2-C=), 8.27 (s, 1H, C-2H); anal. calcd. for $C_{13}H_{12}N_4O_2S_2$ (320): C, 48.75; H, 3.75; N, 17.50; found: C, 48.56; H, 3.57; N, 17.36.

N′[(4-Substitutedphenyl)methylene]-2-[5,6,7,8-tetrahydro[1]benzothieno[2,3-D]-pyrimidin-4-yl-oxy]-acetohydrazide (11a–c)

The hydrazide **2** (10 mmol; 2.78 g) and aromatic aldehydes, namely benzaldehyde, p-chlorobenzaldehyde, and salicylaldehyde (10 mmol), in ethanol (30 mL) were heated under reflux for 3–7 h. A solid product was precipitated during reflux, which was filtered off, washed well, dried and then recrystallized from a suitable solvent to afford **11a–c**, respectively.

11a, white crystals; m.p: 256–258°C; solvent of crystallisation ethanol, yield: 51.3%; anal. calcd. for $C_{19}H_{18}N_4O_2S$ (366): C, 62.29; H, 4.92; N, 15.30; found: C, 62.41; H, 5.09; N, 15.46.

11b, white crystals; m.p: 261–263°C; solvent of crystallisation n-butanol, yield: 45.4%; anal. calcd. for $C_{19}H_{17}ClN_4O_2S$ (400.5): C, 56.93; H, 4.24; Cl, 8.86; N, 13.98; found: C, 56.73; H, 4.06; Cl, 8.67; N, 13.80.

11c, pale yellow crystals; m.p. 272–2744°C; solvent of crystallisation dioxane; yield: 54.2%; anal. calcd. for $C_{19}H_{18}N_4O_3S$ (382): C, 59.69; H, 4.71%; N, 14.66; found: C, 59.55; H, 4.53; N, 14.49.

IR of **11a–c**: ν 3444 and 3432 (OH), 3231 and 3185 (NH), 3088 and 3062 (CH_{ar}), 2986 and 2937 (CH_{al}), 1674 and 1668 (CO), and 1618 and 1616 cm^{-1} (C=N). ^{1}H-NMR of **11c** (DMSO-d_6): the protons of —N=CH, —CONH, —O—CH_2CO, and phenolic —OH groupings in the two isomers appear twice. In the *E*-isomer, protons are more deshielded due to H-bonding: δ 1.79 (m, 4H, C-6 and C-7H), 2.77 (s, 2H, C-5H), 2.87 (s, 2H, C-8H), 5.18 and 4.78 (s, 2H, O-CH_2CO), 7.77–6.88 (m, 4H, Ar-H), 8.33 (s, 1H, C-2H of tetrahydrobenzothienopyrimidine moiety), 8.46 and 8.39 (s, 1H, N=CH), 10.96 and 10.10 (s, 1H, NH), 12.12 and 11.74 (s, 1H, OH).

4-{[5-Phenyl-1,3,4-oxadiazol-2-yl]methoxy}-5,6,7,8-tetrahydro[1]benzothieno[2,3-d-]pyrimidine (12a) and 4-{[2-(4-Chlorophenyl)-1,3,4-oxadiazol-5-yl]methoxy}-5,6,7,8-tetrahydro[1]benzothieno[2,3-D]pyrimidine (12b)

A mixture of acetohydrazide **2** (10 mmol; 2.78 g) and benzoic acid acid and/or 4-chlorobenzoic (10 mmol) in $POCl_3$ (40 mL) was heated on a

water bath under reflux for 5–8 h and left to cool; the reaction mixture was then treated with ice water to afford an oily substance, which, on trituration with ethanol, gave solid products.

12a, white crystals; m.p: 188–190°C; solvent of crystallisation ethanol; yield: 33.3%; anal. calcd. for $C_{19}H_{16}N_4O_2S$ (364): C, 62.64; H, 4.40; N, 15.38; found: C, 62.45; H, 4.23; N, 15.22.

12b, white crystals; m.p.: 228–230°C; solvent of crystallisation benzene; yield: 58.6%; anal. calcd. for $C_{19}H_{15}ClN_4O_2S$ (398.5): C, 57.21; H, 3.76; Cl, 8.91; N, 14.05; found: C, 56.99; H, 3.64; Cl, 8.72; N, 13.86.

IR spectra of **12a**,**b**: ν 3068 (CH_{ar}), 2933 (CH_{al}), 1675 cm^{-1} (C=N); ^{1}H-NMR (DMSO-d_6) of **12a**: δ 1.77 (m, 4H, C-6 and C-7 H), 2.76 (br.s, 2H, C-5H), 2.84 (br.s, 2H, C-8H), 5.54 (s, 2H, OCH_2-C=N), 7.99–7.60 (m, 5H, Ar-H), 8.53 (s, 1H, C-2H).

Reaction of Schiff's Bases 11a,b with Bromine; Formation of 12a & b

A solution of 0.25 mL of bromine in 1.5 mL of acetic acid was added dropwise to a solution of Schiff's bases **11a** and/or **11b** (5 mmol) in 10 mL of acetic acid and excess anhydrous sodium acetate (4 g). The reaction mixture was stirred for 1 h, then poured onto ice water and neutralized by Na_2CO_3 solution. The solid product was filtered off, washed, dried, and then recrystallized from a suitable solvent yielding **12a** and **b**, respectively.

4-[2-(4-Chlorophenyl)-4-oxo-3H-1,3-thiazol-3-yl)-oxyacetamido]-5,6,7,8-tetrahydro[1]-benzothieno-[2,3-d]pyrimidine (13)

An equimolar mixture of Schiff's base **11b** (10 mmol; 3.66 g) and thioglycollic acid (10 mmol; 1 mL) in 60 mL of dry benzene was refluxed for 8 h. Most of the solvent was evaporated, and the reaction mixture was left to cool; the solid product that separated out was filtered off and washed with light petroleum (60–80°C). Crystallization of the crude product from benzene afforded **13** as white crystals; m.p: 210–212°C; yield: 48.94%. IR: ν 3424 (OH), 3199 (NH), 1720 (C=O of cyclic five membered amide), 1685 (C=O of acyclic amide), 1650 cm^{-1} (C=N). MS: m/e: 474 ($M^{+\cdot}$, 3.4), 249 (6.1), 248 (16.5), 247 (100), 219 (77.4), 189 (38.5), 163 (8.7), 162 (7.6), 160 (4.0), 142 (3.2), 126 (1.5), 122 (16.13) and 77 (16.2); anal. calcd. for $C_{21}H_{19}ClN_4O_3S_2$ (474.5): C, 53.11; H, 4.00; Cl, 7.48; N, 11.80; found: C, 52.98; H, 3.89; Cl, 7.26; N, 11.63.

4-[(1,2,3,4-Oxatriazol-5-yl)methoxy]-5,6,7,8-tetrahydro[1]benzothieno[2,3-d]pyrimidine (14)

To an ice-cold solution of acetohydrazide **2** (10 mmol; 2.78 g) in 10 mL of acetic acid (50% w/v) and $NaNO_2$ (0.76 g in 10 mL of H_2O) was added dropwise, the reaction mixture was stirred for 1 h and allowed to stand for 2 h at r.t. The deposited solid product was filtered off by suction, dried, and then recrystallized from benzene to give **14** as a white solid; m.p: 239–240°C; yield: 37.37%. IR: ν 3373 (NH), 3056 (CH_{ar}), 2932 (CH_{al}), 1669 (C=N) and 1648 (N=N); ^{1}H-NMR (DMSO-d_6) : δ 1.78 (m, 4H, C-6 and C-7 H), 2.79 (br.s, 2H, C-5H), 2.82 (br.s, 2H, C-8H), 5.52 (s, 2H, OCH_2-C=N), 6.62 (s, 1H, olefinic HC=C, enimine), 7.78 (s, 1H, NH enimine), 8.53 (s, 1H, C-2H). MS: m/e : 290 ($M^{+\cdot}$, 3.5), 220 (1.69), 219 (5.90), 206 (100), 205 (24.55), 189 (5.83), 179 (11.05), 177 (17.35) and 70 (2.01). Anal. calcd. for $C_{12}H_{11}N_5O_2S$ (289): C, 49.82; H, 3.83; N, 24.21; found: C, 49.58; H, 3.57; N, 23.99.

N-Ethoxymethylene-2-(5,6,7,8-tetrahydro[1]benzothieno-[2,3-d]pyrimidin-4-yloxy)aceto-hydrazide (15)

The solution of acetohydrazide **2** (5 mmol; 1.39 g) in 10 mL of triethyl orthoformate was heated under reflux on a water bath for 7 h, left to cool, and then poured onto ice water. The solid product that separated out was filtered off and crystallized from a benzene/ethanol mixture afforded the product **15** as white crystals; m.p: 141–143°C; yield: 22.7%. IR: ν 3503 (OH), 3224 (NH), 3049 (CH^{ar}), 2979 (CH_{al}), 1677 (CO acyclic amide), 1657 cm^{-1} (C=N); ^{1}H-NMR ($CDCl_3$): δ 1.32 (t, 3H, $CH_2C\underline{H_3}$), 1.85 (br.s, 4H, C-6H and C-7H of tetrahydrobenzothienopyrimidine moiety), 2.78 (br.s, 2H, C-5H), 2.99 (br.s, 2H, C-8H), 4.15 (q, 2H, $C\underline{H_2}CH_3$), 6.51 and 8.91 (two s, 1H, =N-$\underline{NH}$-C=O $\rightleftharpoons$ =N-N=C-$\underline{OH}$) and 8.06 (s, 1H, C-2H); anal. calcd. for $C_{15}H_{18}N_4O_3S$ (334): C, 53.89; H, 5.39; N, 16.77; found: C, 53.69; H, 5.26; N, 16.59.

(5,6,7,8-Tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-yloxy)-acetic Acid (16)

The solution of acetohydrazide **2** (5 mmol; 1.39 g) in 15 mL of formic acid was heated under reflux for 6 h, left to cool and poured onto ice water; the solid product that separated out was filtered off. Crystallization from benzene yielded the title product **16** as white crystals; m.p: 240–242°C; yield: 69.3%. IR: ν 3446 (OH), 3053 (CH_{ar}), 2856 (CH_{al}), 1729 (CO acid), 1670 (C=N) with the disappearance of ν_{NH}; ^{1}H-NMR (DMSO-d_6) : δ 1.70 (br.s, 4H, C-6 and C-7H), 2.76 (br.s, 2H, C-5H), 2.87 (br.s, 2H, C-8H),

4.71 (s, 2H, OCH_2CO), 8.32 (s, 1H, C-2H), 13.08 (br.s, 1H, COOH); anal. calcd. for $C_{12}H_{12}N_2O_3S$ (264): C, 54.55; H, 4.55; N, 10.60; found: C, 54.35; H, 4.47; N, 10.44.

Ethyl 3-{[(5,6,7,8-Tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-yloxy)acetyl]hydrazono}-butanoate (17)

A mixture of hydrazide **2** (10 mmol; 2.78 g) and ethyl acetoacetate (10 mmol; 1.3 mL) in NaOEt (0.23 g of Na metal in 30 mL of absolute ethanol) was heated under reflux for 8 h. Most of the solvent was evaporated, left to cool, and acidified with cold diluted HCl. The solid product was filtered off, dried, and then recrystallized from benzene to give **17** as white solid; m.p: 288–290°C; yield: 44.61%. IR: ν 3219 (NH), 3050 (CH_{ar}), 2935 (CH_{al}), 1735 (C=O ester), 1682 cm^{-1} (C=O acyclic amide); ^{1}H-NMR (DMSO-d_6): δ 1.21 (t, 3H, $OCH_2C\underline{H}_3$), 1.77 (br.s, 4H, C-6 and C-7H), 1.97 (s, 3H, N=C-CH_3), 2.76 (br.s, 2H, C-5H), 2.85 (br.s, 2H, C-8H), 3.37 (s, 2H, N=C-CH_2-CO), 4.10 (q, 2H, O-C$\underline{H}_2$-CH_3), 5.00 (s, 2H, O-CH_2CO), 8.27 (s, 1H, C-2H) and 10.82 and 7.38 (2s, 1H, of lactam-lactim mixture, NH-C=O $\rightleftharpoons$ N=C-OH); anal. calcd. for $C_{18}H_{22}N_4O_4S$ (390): C, 55.38; H, 5.64; N, 14.36; found: C, 55.19; H, 5.48; N, 14.23.

(5,6,7,8-Tetrahydro[1]benzothieno[2,3-d]pyrimidin-4-yloxy)-acetic Acid (16)

The solution of derivative **17** (10 mmol; 3.9 g) in 50 mL of NaOH (20%) was heated under reflux for 4 h. Most of the solvent was evaporated and left to cool. Acidification with cold diluted HCl produced a solid product, which was filtered off, dried, and then recrystallized from benzene to give **16** in a 71.8% yield.

REFERENCES

[1] G. E. Robinson and C. J. Squire, *Eur. Pat*. 253,507 (1988); *C.A*., **109,** 6318 (1988).
[2] F. E. Janssens, I. G. Torremans, J. F. Hens, and T. T. J. M. Van Offenwert, *Eur. Pat*. 144,101 (1985); *C.A*., **104,** 68856 (1986).
[3] A. P. Vingoardoff, N. P. Peet, and S. Sunder, *Eur. Pat*. 234,557 (1987); *C.A*., **108,** 6042 (1988).
[4] S. E. DeLaszlo, A. A. Patchett, E. E. Allen, and W. J. Greenle, *Eur. Pat*. 502,725 (1992); *C.A*., **118,** 22249 (1992).
[5] Z. H. Khalil and A. A. Geies, *Phosphorus, Sulfur, and Silicon*, **60,** 223 (1991).
[6] R. Boehm, G. Hanbold, R. Pech, and G. Laban, *Ger. Pat*. 226,893 (1985); *C.A*. **104,** 186437 (1986).
[7] G. Wagner, H. Vieweg, and S. Leistner, *Pharmazie*, **48,** 667 (1993).
[8] M. Wiesenfeldt, K. H. Etzbach, P. Hofmeister, C. Kueyast, and K. O. Westpalen, *Eur. Pat*. 447,891 (1991); *C.A*. **115,** 256224 (1991).

[9] H. M. F. MadKour, M. A. I. Salem, T. M. AbdelRahman, and M. E. Azab, *Heterocycles*, **38,** 57 (1994).
[10] A. S. Hamad and M. E. Azab, *Phosphorus, Sulfur, and Silicon*, **173,** 105 (2001).
[11] M. E. Azab, G. A. M. El-Hag Ali, and A. F. Abdel-Wahab, *Acta Chemica Pharmaceutica*, **53,** 213 (2003).
[12] M. A. I. Salem, E. A. Soliman, M. B. Smith, M. R. Mahmoud, and M. E. Azab, *Phosphorus, Sulfur, and Silicon*, **179,** 61 (2004).
[13] H. M. F. MadKour, *ARKIVOC*, 36 (2004).
[14] H. M. F. MadKour, *Chem. Pap*., **56,** 314 (2002).
[15] H. M. F. MadKour, M. R. Mahmoud, A. M. Sakr, and M. M. Habashy, *Scientia Pharmazeutica*, **69,** 33 (2001).
[16] H. M. F. MadKour, S. A. Shiba, H. M. Sayed, and A. A. Hamed, *Sulfur Letters*, **24,** 151 (2001).
[17] H. M. F. MadKour, M. A. I. Salem, E. A. Soliman, and N. F. H. Mahmoud, *Phosphorus, Sulfur, and Silicon*, **170,** 15 (2001).
[18] P. P. Norton, S. Shyam, and J. Robert, *J. Het. Chem.*, **20,** 511 (1983).
[19] K. C. Joshi, Jain, A. Damdi, and K. Sharma, *J. Het. Chem.*, **25,** 1641 (1988).
[20] M. S. Amine, M. A. El-Hashash, and I. A. Attia, *Indian J. Chem.*, **32B,** 577 (1993).
[21] Z. A. Hozien, F. M. Atta, Kh. M. Hassan, A. A. Abdel-Wahab, and S. A. Ahmad, *Synth. Comm*., **26,** 3733 (1996).
[22] N. Chau, Y. Saegusa, and Y. Lwakura, *J. Het. Chem*., **19,** 541 (1982).
[23] R. W. Young and K. H. Wood, *J. Am. Chem. Soc*., **77,** 400 (1955).
[24] M. M. El-Kerdawy, A. E. M. Ismaiel, M. M. Gineinah, and R. A. Glennon, *J. Het. Chem.*, **27,** 494 (1990).
[25] M. M. Dutta, B. N. Goswami, and J. C. S. Kataky, *J. Het. Chem*., **23,** 793 (1986).
[26] C. J. Shishoo, M. B. Devani, G. V. Ullas, S. A. Ananhan, and V. S. Bhadti, *J. Het. Chem*., **25,** 615 (1988).
[27] A. B. El-Gassar and M. A. Hassan, *Molecules*, **5,** 835 (2000).
[28] V. J. Ram, H. K. Pandy, and A. Vlietinck, *J. Het. Chem.*, **18,** 1277 (1981).
[29] V. I. Shvedov, V. K. Ryzhkova, and A. N. Grinev, *Khim. Geterotsikl. Soedin*. **3,** 459 (1967); *C.A*., **68,** 50519h (1968).