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New Route for the Synthesis of Pyrazole, Triazole, Triazine, and Triazepine Derivatives

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New Route for the Synthesis of Pyrazole, Triazole, Triazine, and Triazepine Derivatives

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Abstract: N,N′-Diphenylpiperidine-1-carbohydrazonamide **1** was prepared and treated with halo compounds, active nitriles, diethylhy malonate, ketones, CS_2, phenylisocyanate, phenylisothiocyanate, LR, ethyl 2-cyano-3,13-dithiomethylacetate, and benzylidenenitriles to give the corresponding triazines **2–4**, pyrazoles **5** and **6**, triazoles **7**, **8**, and **10**, triazaphosphole **11**, and triazepines **12–14**, respectively.

Keywords: Pyrazoles, triazepines, triazines, triazoles

Triazole,[1–4] pyrazole,[4,5] triazine,[2,6,7] and triazepine[2,8] derivatives have a wide range of biological activities including anti-angiogenesis, herbicidal effects, antimetastatic effects, and antibacterial and fungicidal properties. As a continuation of our previous work[2–5] on these systems, we report here the synthesis and reactivity of new pyrazole, triazole, triazine, and triazepine derivatives via the reaction of compound **1** with some reagents, hoping to obtain these compounds with enhanced biological activity and medicinal applications.

RESULTS AND DISCUSSION

N,N′-Diphenylpiperidine-1-carbohydrazonamide **1** was prepared via the reaction of 1-piperidinethiocarboxanilide[9,10] with phenylhydrazine. Its IR

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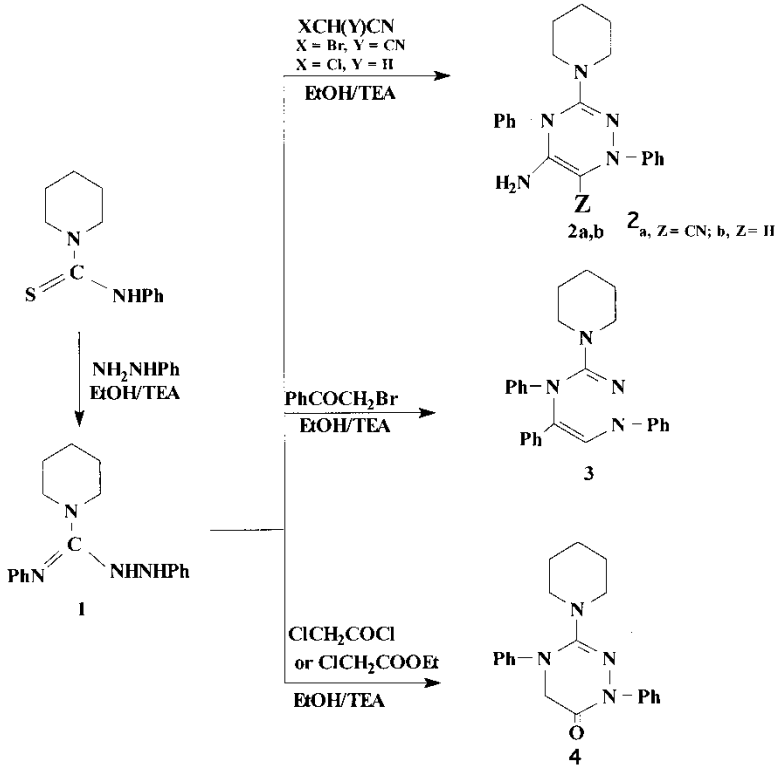
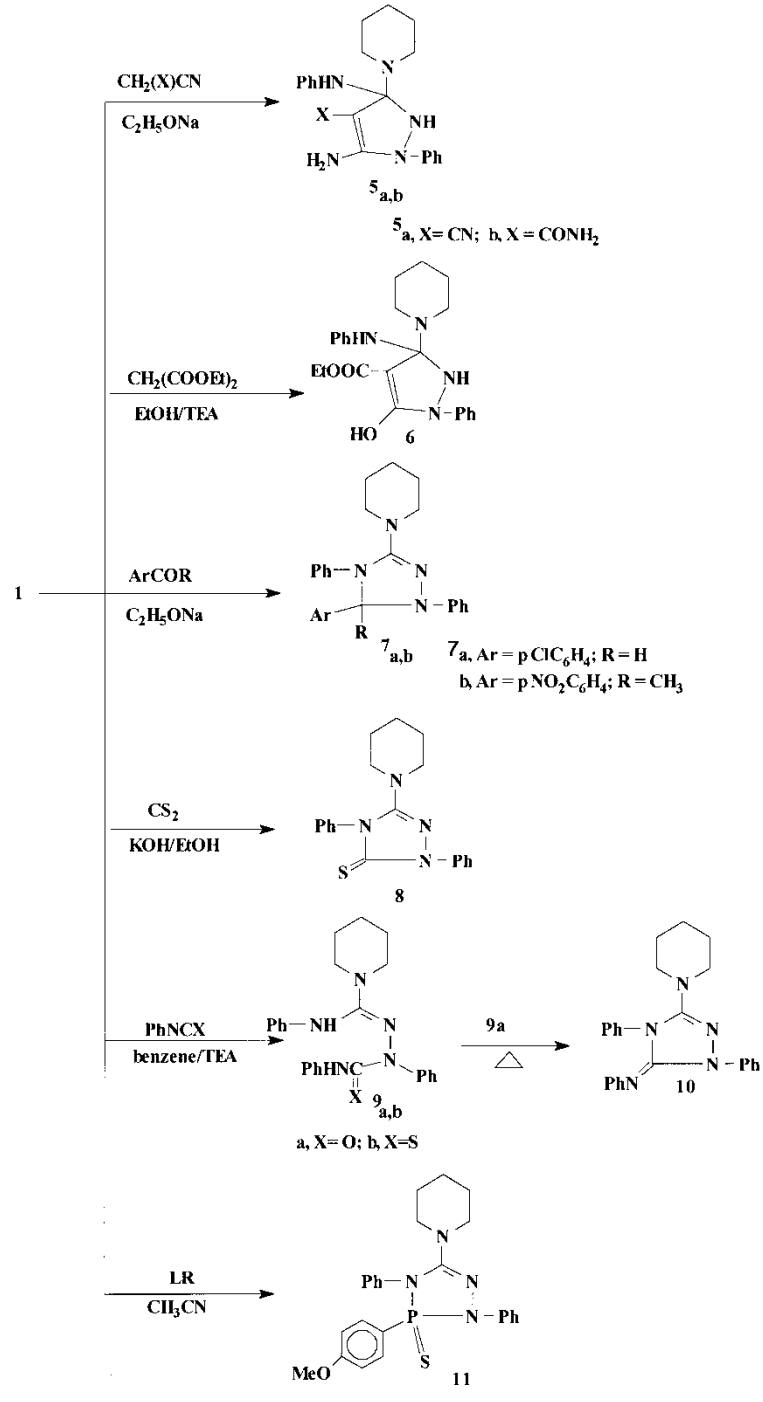
spectrum showed absorption peaks at 3275 and 3169 cm^{-1} corresponding to two NH groups.

The reaction of compound **1** with active halo compounds (namely, bromomalononitrile, chloroacetonitrile, phenacyl bromide, ethyl chloroacetate, or chloroacetyl chloride) in the presence of TEA gave the corresponding 5-amino-6-cyano-l,4-diphenyl-3-(piperidin-l-yl)-1,4-dihydro[1,2,4]triazine **2a**, 5-amino-1,4-diphenyl-3-(piperidin-1-yl)-1,4-dihydro[1,2,4]triazine **2b** 1,4,5-triphenyl-3-(piperidin-1-yl)-1,4-dihydro[1,2,4]triazin **3**, and 1,4-diphenyl-3-(piperidin-1-yl)-1,4,5,6-tetrahydro[1,2,4]triazin-6-one **4**, respectively. The reaction pathway was assumed to proceed via alkylation of the NH group followed by nucleophilic attack of the second NH group at the CN or the C═O groups with elimination of H_2O, EtOH, or HCl molecule (c.f. Scheme 1).

Compound **1** was reacted with malononitrile, cyanoacetamide, or diethylmalonate in the presence of sodium ethoxide to give 5-amino-3-anilino-1-phenyl-3-(piperidin-1-yl)-2,3-dihydro-1H-pyrazole-4-carbonitrile **5a**, 5-amino-3-anilino-1-phenyl-3-(piperidin-l-yl)-2,3-dihydro-1H-pyrazole-4-



Scheme 1.



Scheme 2.

carboxamide **5b**, and ethyl 3-anilino-5-hydroxy-1-phenyl-3-(piperidin-1-yl)-2,3-dihydro-1H-pyrazole-4-carboxylate **6**, respectively (c. f. Scheme 2).

Treatment of compound **1** with *p*-chlorobenzaldehyde or *p*-nitroacetophenone in the presence of sodium ethoxide afforded 1-[5-(*p*-chlorophenyl)-1,4-diphenyl-4,5-dihydro-1H-[1,2,4]triazol-3-yl)-piperidine **7a** and 1-[5-methyl-5-(*p*-nitrophenyl)-1,4-diphenyl-4,5-dihydro-1H-[1,2,4]triazol-3-yl)piperidine **7b**, respectively (cf. Scheme 2).

On treatment of compound **1** with carbon disulfide in the presence of KOH, 1,4-diphenyl-3-(piperidin-l-yl)-4,5-dihydro[l,2,4]triazin-5-thione **8** was obtained (cf. Scheme 2).

The reaction of compound **1** with phenyl isocyanate or phenyl isothiocyanate and TEA gave the corresponding urea and thiourea derivatives **9a,b**. Compound **9a** underwent intramolecular cyclization to give triazole derivative **10** on heating in diphenylether (cf. Scheme 2).

The chemistry of Lawesson's reagent (LR) as thiation reagent has been studied, and several papers describe its ring-closure reactions with substrates containing two functional group.[11] Thus, the reaction of compound **1** with LR in boiling acetonitrile yielded 1-[3-(*p*-methoxyphenyl)-2,4-diphenyl-3-sulfido-3,4-dihydro-2H-1,2,4,3-triazaphosphol-5-yl]piperidine **11**. Its IR spectrum showed the following absorption bands at 1610 and 1110 cm^{-1} for the C═N, and P═S groups, respectively (cf. Scheme 2).

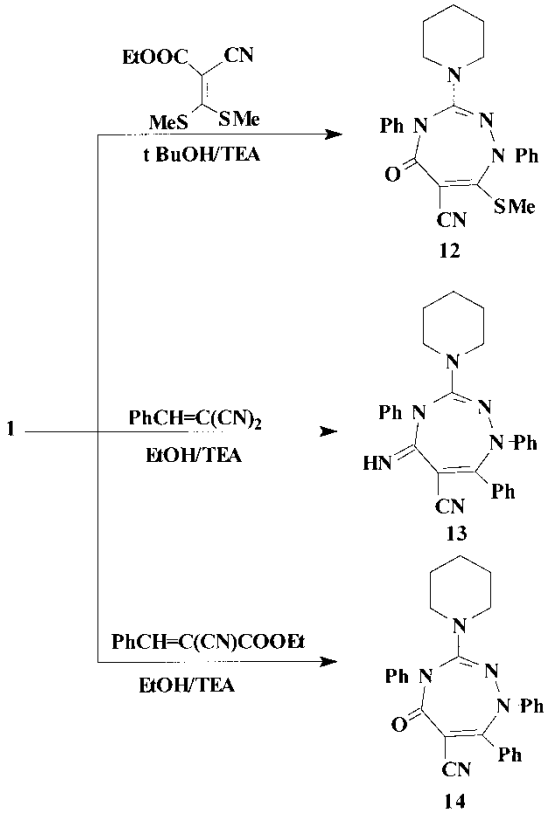
Treatment of compound **1** with ethyl 2-cyano-,3,3-dithiomethylacetate in the presence of TEA gave 7-methylthio-5-oxo-1,4-diphenyll-3-(piperidin-1-yl)-4,5-dihydro-1H-[1,2,4]triazepin-6-yl carbonitrile **12**. Its IR spectrum revealed that the C═O and CN groups have absorption bands at 1696 and 2196 cm^{-1} respectively. The reaction mechanism was assumed to involve an addition of the NH group at the ethylenic bond with elimination of MeSH molecule, followed by a nucleophilic attack of the second NH group at C═O group with elimination of EtOH molecule (cf. Scheme 3).

Finally, the reaction of compound **1** with benzylidene-malononitrile or ethyl benzylidenecyanoacetate in the presence of TEA afforded 6-cyano-5-imino-l,4-diphenyl-3-(piperidin-l-yl)-4,5-dihydro-lH-[l,2,4] triazepine **13** or 6-cyano-5-oxo-1,4-diphenyl-3-(piperidin-1-yl)-4,5-dihydro-1H-[1,2,4]triazepine **14**, respectively. The reaction pathway proceeded via a nucleophilic attack of the NH group to the ethylenic bond followed by a nucleophilic addition of the second NH group to the CN group or the C═O group with elimination of EtOH molecule (cf. Scheme 3).

EXPERIMENTAL

Synthesis of Compounds 1

A mixture of 1-piperidinethiocarboxanilide[9,10] (0.01mol, 2.2 g) and phenylhydrazine (0.01 mol, 1.08 mL) in ethanol (20 mL) was refluxed for 15 h. The



Scheme 3.

precipitated product **formed on hot** was filtered off and crystallized (cf. Scheme 1).

Synthesis of Compounds 2–4

Compound **1** (0.01 mol, 2.93 g) [halo compound, namely bromomalononitrile (1.44 g), chloroacetonitrile (0.65 mL), phenacyl bromide (1.99 g), ethyl chloroacetate (1.22 mL), or chloroacetyl chloride (1.1 mL) and TEA (1.4 mL)] was refluxed in ethanol (20 mL) for 4 h. On cooling, the formed precipitate was filtered off and crystallized (cf. Scheme 1).

Synthesis of Compounds 5a,b and 6

Compound **1** (0.02 mol, 0.58 g), malononitrile (0.13 g), cyanoacetamide (0.17 g), diethyl malonate (0.32 mL), and sodium ethoxide (0.06 g of Na in

30 mL ethanol) were refluxed for 3 h. On cooling, the reaction mixture was poured into ice-cold water (50 mL) containing HCl (5 mL). The precipitated solid was filtered, dried, and crystallized (cf. Scheme 2).

Synthesis of Compounds 7a,b

A mixture of compound **1** (0.003 mol, 0.87 g) and *p*-chloro-benzaldehyde (0.003 mol, 0.42 g) or *p*-nitroacetophenone (0.003 mol, 0.49 g) in sodium ethoxide solution (0.003 mol, 0.05 g of Na in 25 mL of ethanol) was refluxed for 4 h. On cooling, the reaction mixture was poured into ice-cold water (40 mL) containing HCl (5 mL). The precipitated solid was filtered off, dried, and crystallized (cf. Scheme 2).

Synthesis of Compound 8

A mixture of compound **1** (0.02 mol, 0.58 g), carbon disulphide (0.02 mol, 0.15 mL), potassium hydroxide (0.02 mol, 0.11 g in 2 mL of water), and ethanol (30 mL) was refluxed for 4 h. On cooling, the reaction mixture was poured into ice-cold water (50 mL) containing HCl (5 mL). The precipitated solid was filtered off, dried, and crystallized (cf. Scheme 2).

Synthesis of Compounds 9a,b

Compound **1** (0.02 mol, 0.58 g), phenylisocyanate (0.23 mL) or phenylisothiocyanate (0.27 mL), and triethylamine (0.28 mL) were dissolved in dry benzene (20 mL) and refluxed for 10 h. The reaction mixture was left to cool; the formed precipitate was filtered off and crystallized (cf. Scheme 2).

Synthesis of Compound 10

Compound **9a** (0.01 mol, 0.41 g) was suspended in diphenylether (10 mL) and refluxed for 1 h. On cooling, the formed precipitate was filtered off and crystallized (cf. Scheme 2).

Synthesis of Compound 11

A mixture of compound **1** (0.01 mol, 2.94 g), LR (0.01 mol, 2.02 g), and acetonitrile (40 mL) was refluxed for 12 h until no more of the reactants could be detected by thin-layer chromatography (TLC). The solvent was evaporated to dryness under reduced pressure. The residue was triturated with ethanol. The separated solid was filtered off and crystallized (cf. Scheme 2).

Synthesis of Compound 12

Compound **1** (0.02 mol, 5.8 g), ethyl 2-cyano-3,3-dithio-methylacetate (5.2 g), and triethylamine (2.8 mL) were refluxed in ethanol (20 mL) for 3 h. The reaction mixture was left to cool; the formed precipitate was filtered off, dried, and crystallized (cf. Scheme 3).

Synthesis of Compounds 13 and 14

Compound **1** (0.02 mol, 0.58 g), benzylidenemalononitrile (0.31 g) or ethyl benzylidenecyanoacetate (0.4 g), and triethylamine (0.3 mL) were refluxed in DMF (40 mL) for 3 h. The reaction mixture was left to cool and poured into ice-cold water (50 mL) containing HCl (5 mL). The formed precipitate was filtered off and crystallized (cf. Scheme 3).

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