A Convenient and Efficient Conversion of 4-Aminobenzophenone into some new 1,2,3-Triazole and Benzothiazole Derivatives

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Several heterocyclic systems such as 1,2,3-triazoles (**5-9**), pyrimidotriazoles (**10-13**), benzothiazole (**16**), thiazolo (**17**), and pyrimidinone derivative (**18**) was obtained from 4-aminobenzophenone (**1**) and the appropriate reagents.

Keywords: Synthesis; 1,2,3-Triazole; 1,3,4-Triazole and benzothiazole.

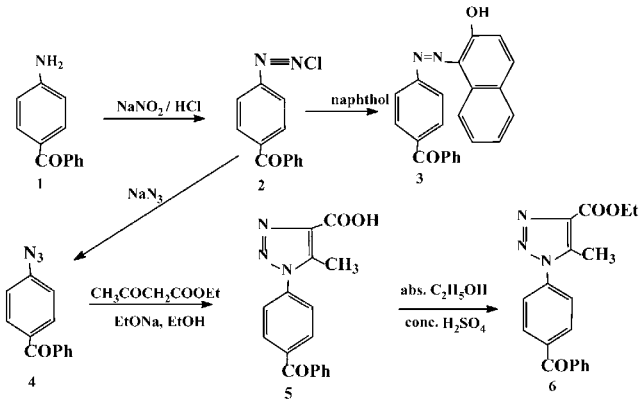
INTRODUCTION

A wide variety of benzothiazole and triazole derivatives have been developed as anticancer agents[1-6] and flavone (*egquercetin*) and isoflavone (*genistien*) isosteres to inhibit PTK enzymes[7] Tricyclazole is a well known fungicide for the control of *Piricularia oryzae* in the prevention of rice blast[8] furthermore, new 1,3,4-triazole derivatives have been reported as potential anticonvulsants[9] and anti-inflammatory and analgesic agents.[10] Taking all the above benefits into consideration and in continuation of our work on the synthesis of many fused heterocyclic systems[11-17] we investigate the use of 4-aminobenzophenone for the synthesis of these fused heterocyclic systems with the aim of investigating their antimicrobial activities.

RESULTS AND DISCUSSION

Diazotization of 4-aminobenzophenone **1** by nitrous acid at 0-5 °C led to the formation of 4-benzoylphenyldiazonium chloride **2**, which when coupled with β-naphthol yielded 4-benzoylphenylazo-β-naphthol **3**. Reaction of the diazonium salt **2** with sodium azide produced 4-azidobenzophenone **4**. It was reported that the azide compound can be cyclized using ethyl acetoacetate to furnish 1,2,3-triazole derivative.[18,19] In a similar fashion azide compound **4** was cyclized with ethyl acetoacetate in the presence of sodium ethoxide to afford 5-methyl-1-[4′-benzophenone]-1,2,3-triazole-4-carboxylic acid **5**. Esterification of the carboxylic compound **5** was achieved with abs.ethanol and catalyzed by conc. H_2SO_4 to afford the corresponding ethyl ester **6** (Scheme I).

Scheme I



Also, the azide **4** was reacted with active nitriles, namely *p*-nitrobenzylcyanide and malonodinitrile in sodium ethoxide to produce 4-amino-1-[4′-benzophenone]-5-*p*-nirophenyl-1,2,3-triazole **7** and 4-amino-1-[4′-benzophenone]-5-cyano-1,2,3-triazole **8**. Compound **8** was reacted with ethylene diamine to give imidazoyl-1,2,3-triazole derivative **9** which was cyclized to 9-[4′-benzophenone]-imidazopyrimidotriazole **10** through reaction with triethyl orthoformate. The cyano compound **8** was cyclized to pyrimidotriazoles **11-13** on treatment with formamide, CS_2 in alc. KOH and/or phenyl isothiocyanate in pyridine, respectively (Scheme II).

4-Benzoyl-anilinehydrochloride **14** was prepared from 4-aminobenzophenone **1** by boiling with conc. HCl, and this

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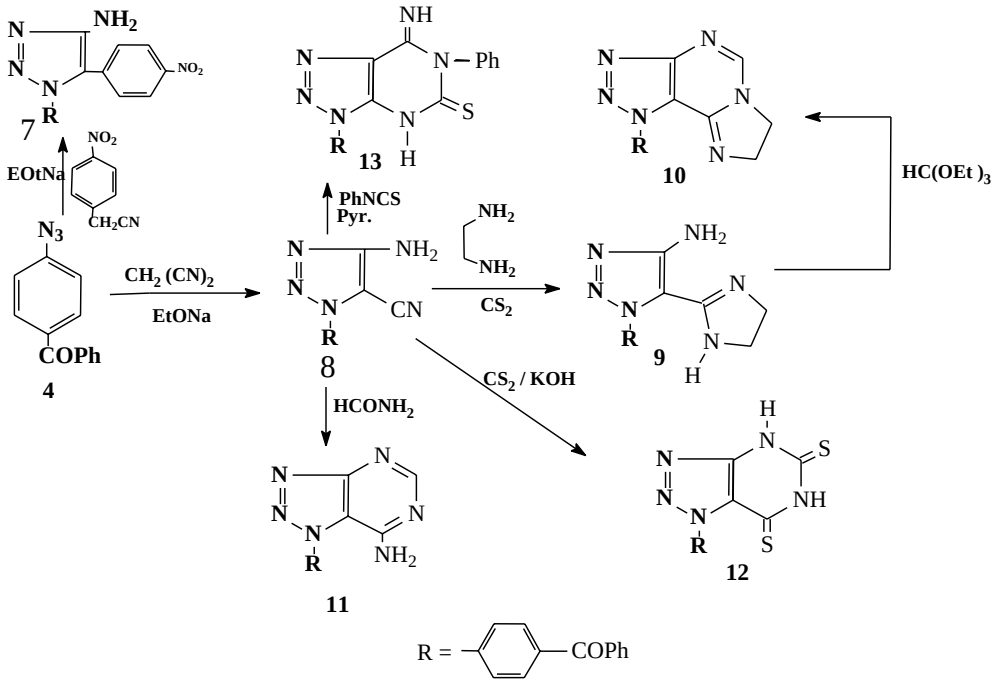
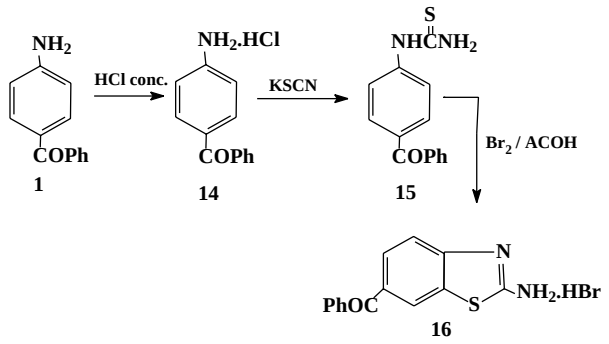
Scheme II



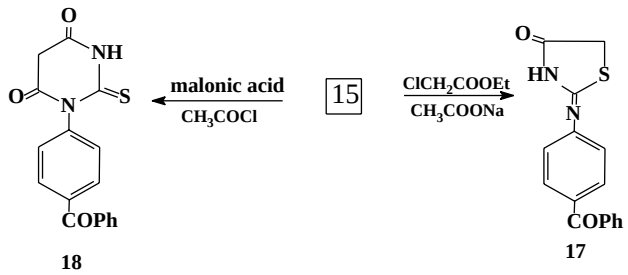
was reacted with potassium thiocyanate to give *p*-thioureidobenzophenone **15**. The latter compound in acetic acid solution was brominated and cyclized to 2-amino-6-benzoylbenzothiazole hydrobromide **16** on treatment with bromine (Scheme III).

Scheme III



Thioureido compound **15** was cyclized to thiazolo derivative **17** and/or to pyrimidinone derivative **18** through reactions with ethyl chloroacetate in the presence of fused sodium acetate and/or with malonic acid in the presence of acetylchloride, respectively (Scheme IV).

Scheme IV



EXPERIMENTAL

Melting points were determined on a Gallen Kamp melting point apparatus and were uncorrected. IR spectra were recorded on a Pye-Unicam SP^3-100 spectrophotometer using KBr wafer technique. ^{1}H NMR spectra were recorded on a 90 MHz Varian EM-390 NMR spectrometer in a suitable deutreated solvent (TMS) as the internal standard. Elemental analyses were determined on a Perkin-Elmer 240 C microanalyzer, and all compounds gave results in an acceptable range. Melting points, yields and spectroscopic data of compounds **2-18** are listed in Tables **1** and **2**.

Table 1. Physical constants of compounds **2-18**

Comp. No	M.P °C (Yield %)	Formula Mol.Wt	Comp. No	M.P °C (Yield %)	Formula Mol.Wt
2	-	$C_{13}H_9N_2OCl$ 244.5	**11**	> 300 (68-71)	$C_{17}H_{12}N_6O$ 316
3	230 (80-83)	$C_{23}H_{16}N_2O_2$ 352	**12**	> 310 (63-65)	$C_{17}H_{11}N_5OS_2$ 365
4	135* (83-85)	$C_{13}H_9N_3O$ 223	**13**	165 (70-72)	$C_{23}H_{16}N_6OS$ 424
5	192 (76-80)	$C_{17}H_{13}N_3O_3$ 307	**14**	182 (66-69)	$C_{13}H_{12}NOCl$ 233.5
6	142 (75-76)	$C_{19}H_{17}N_3O_3$ 335	**15**	120 (65-70)	$C_{14}H_{12}N_2OS$ 256
7	> 300 (84-88)	$C_{21}H_{15}N_5O_3$ 385	**16**	161 (69-71)	$C_{14}H_{11}N_2OSBr$ 335
8	235 (90-92)	$C_{16}H_{11}N_5O$ 289	**17**	202 (65-68)	$C_{16}H_{12}N_2O_2S$ 296
9	143 (77-78)	$C_{18}H_{16}N_6O$ 332	**18**	210 (68-70)	$C_{17}H_{12}N_2O_3S$ 324
10	230 (61-65)	$C_{19}H_{14}N_6O$ 342			

*: decomposition.

Table 2. Spectral data of compounds **3-18**

Comp. No	IR (ν cm $^{-1}$) / ^{1}HNMR (δ ppm)
3	1670 (N=N), 1660 (C=O), 1590 (C=N); (DMSO-d_6): δ 7.2-8.0 (m, 15H, Ar-H), 10.2 (s, 1H, OH).
4	2230 (azide N_3), 1660 (C=O); (DMSO-d_6): δ 7.2-8.1 (m, 9H, Ar-H).
5	3450-3500 (acid, OH), 2980 (CH-alph.), 1700, 1650 (C=O); (DMSO-d_6): δ 2.3 (s, 3H, CH_3), 7.4-8.00 (m, 9H, Ar-H), 10.5 (s, 1H, OH).
6	2980 (CH-alph.), 1720, 1650 (C=O); ($CDCl_3$): δ 1.35 (t, 3H, CH_3), 2.45 (s, 3H, CH_3 triazole), 4.2 (q, 2H, CH_2), 7.4-8.2 (m, 9H, Ar-H).
7	3300, 3200 (NH_2), 1650 (C=O); (DMSO-d_6): δ 7.22 (s, 2H, NH_2 disappeared by D_2O), 7.3-8.1 (m, 13H, Ar-H).
8	3300, 3200 (NH_2), 2220 (CN), 1640 (C=O), 1590 (C=N); (DMSO-d_6): δ 7.2 (s, 2H, NH_2 disappeared by D_2O), 7.4-8.0 (m, 13H, Ar-H).
9	3400, 3300, 3200 (NH, NH_2), 1650 (C=O); (DMSO-d_6): δ 4.1 (s, 4H, $2CH_2$), 7.15 (s, 2H, NH_2 disappeared by D_2O), 7.2-7.9 (m, 9H, Ar-H), 10.1 (s, 1H, NH).
10	1695 (C=O), 1610 (C=N); (CF_3COOD): δ 4.24 (s, 4H, $2CH_2$), 7.3-8.1 (m, 9H, Ar-H), 10.1 (s, 1H, CH).
11	3340, 3240 (NH_2), 1665 (C=O), 1600 (C=N); (DMSO-d_6): δ 7.1 (s, 2H, NH_2 cancelled by D_2O), 7.5-8.4 (m, 9H, Ar-H), 9.9 (s, 1H, CH).
12	3200-3420 (NH), 1665 (C=O), 1210 (C=S); (CF_3COOD): δ 7.5-8.4 (m, 9H, Ar-H).
13	3200 (NH), 1665 (C=O), 1210 (C=S); (DMSO-d_6): δ 7.5-8.4 (m, 9H, Ar-H), 9.9 (s, 1H, NH).
14	3450-3500 (b, acid, NH_2), 1660 (C=O).
15	3400, 3200 (NH, NH_2), 1660 (C=O), 1220 (C=S); (DMSO-d_6): δ 7.35-8.15 (m, 9H, Ar-H), 9.55 (s, 1H, NH).
16	3450, 3310 (b, acid, NH_2), 1645 (C=O), 1610 (C=N); (DMSO-d_6): δ 7.2-8.1 (m, 8H, Ar-H).
17	3280-3120 (NH), 1720, 1650 (2C=O), 1620 (C=N); (DMSO-d_6): δ 4.15 (s, 2H, CH_2), 7.1-8.1 (m, 9H, Ar-H), 10.2 (s, H, NH).
18	3220-3100 (NH), 1710, 1645 (C=O); (DMSO-d_6): δ 4.25 (s, 2H, CH_2), 7.2-8.1 (m, 9H, Ar-H), 9.75 (s, H, NH).

Synthesis of 4-Benzoyl-phenyldiazonium chloride (2) & Synthesis of 4-benzoyl-phenylazo-β-naphthol (3)

The title compounds were prepared by treatment of 4-aminobenzophenone **1** (0.015 mol) with hydrochloric acid (25 mL) while adding dropwise sodium nitrite solution at 0-5 °C and stirring for one hour (afforded the diazonium chloride **2**); β-naphthol (0.015 mol) was added to the latter diazonium salt. An orange solid product was collected.

Synthesis of *p*-Azidobenzophenone (4)

To a cooled stirred solution of diazonium chloride **2** was added a solution of sodium azide (25 mL, 10%) for 30 min, and the resulting solid was filtered and recrystallized from ethanol as yellow crystals.

Synthesis of 5-Methyl-1-[4′-benzophenone]-1,2,3-triazole-4-carboxylic acid (5)

A mixture of azide **4** (0.1 mol), ethyl acetoacetate (0.1 mol) in absolute ethanol (40 mL), and sodium ethoxide solution (20 mL) was refluxed for 4 hr; the white solid which formed on heating was filtered and recrystalized from ethanol.

Synthesis of Ethyl(5-methyl-1-[4′-benzophenone]-1,2,3-triazole)-4-carboxylate (6)

The esterification of **5** was achieved with abs ethanol. A mixture of **5** (0.1 mol) in abs ethanol (40 mL) and concentrated sulfuric acid (5 mL) was refluxed gently for 3 hr, then cooled to room temperature. A white solid was obtained and filtered and recrystalized from ethanol.

Synthesis of 4-Amino-1-[4′-benzophenone]-5-*p*-niro-phenyl-1,2,3-triazole (7)

Sodium ethoxide solution (20 mL) was added dropwise to a stirred solution from a mixture of azide **4** (0.1 mol) and *p*-nitrobenzyl cyanide (0.1 mol) in absolute ethanol (20 mL) over 10 min. at room temperature. The gray solid quickly precipitated and was filtered and recrystallized from ethanol.

Synthesis of 4-Amino-1-[4′-benzophenone]-5-cyano-1,2,3-triazole (8)

Sodium ethoxide solution (20 mL) was added dropwise to a stirred solution contaning azide **4** (0.1 mol) and malonodinitrile (0.1 mol) in absolute ethanol (25 mL) over 10 min. at room temperature. The buff solid quickly precipitated and was filtered and recrystallized from ethanol.

Synthesis of 4-Amino-1-[4′-benzophenone]-5-(amidazol-2-yl)-4″,5″-dihydro-1,2,3-triazole (9)

To a mixture of **8** (0.01 mol) and ethylenediamine (10 mL) was added dropwise CS_2 (1 mL). The resulting reaction mixture was heated on a steam bath for 3 hr. The cold reaction mixture was poured into cold water and left to stand for 2 hr. The greenish needles solid precipitate was filtered and recrystallized from ethanol.

Synthesis of 9-[4′-Benzophenone]-imidazopyrimido-2,4,5-trihydro-1,2,3-triazole (10)

To a mixture of **9** (0.01 mol) and triethyl orthoformate (10 mL) a few drops of acetic acid were added. The reaction mixture was heated under reflux for 4 hr. The solid product thus formed on heating was filtered and recrystallized from acetic acid as pale yellow crystals.

Synthesis of 5-[4′-Benzophenone]-4-amino-(2*H*)-pyrimido[4,5-d]-1,2,3-triazole (11)

A solution of **8** (0.5 g) in formamide (10 mL) was refluxed for 2 hr, then allowed to cool; the yellow precipitate was filtered and recrystallized from ethanol.

Synthesis of 5-[4′-Benzophenone]-2,4-dimercapto-(1,3*H*)-pyrimido[4,5-d]-1,2,3-triazole (12)

A mixture of **8** (0.01 mol) and carbon disulfide (8 mL) in KOH (30 mL, 20%) was refluxed on a steam bath for 5 hr, then allowed to cool. The solid product thus formed on neutralization by acetic acid was recrystallized from ethanol as yellow crystals.

Synthesis of 7-[4′-Benzophenone]-3-mercapto-2-phenyl-4-emino(1,3*H*)-pyrimido[4,5-d]-1,2,3-triazole (13)

To a solution of **8** (0.01 mol) in pyridine (20 mL) added phenyl isothiocyanate (0.01 mol) and the mixture was refluxed for 4 hr. After cooling, the solid product was recrystallized from ethanol as buff crystals.

Synthesis of 4-Benzoyl-anilinehydrochloride (14)

A solution of 4-aminobenzophenone **1** (1 g) in conc. HCl (10 mL) was refluxed for one hour, then allowed to cool; the white solid product was filtered and dried in air.

Synthesis of *p*-thioureidobenzophenone (15)

Potassium thiocyanate soultion (0.01 mol in 10 mL of H_2O) was added dropwise to a stirred solution of **14** (0.01

mol) over 10 min. at room temperature. The deep yellow precipitate was filtered and recrystallized from ethanol.

Synthesis of 2-Amino-6-benzoylbenzothiazole hydrobromide (16)

To a solution of thioureido **15** (0.01 mol) in acetic acid (25 mL) was added dropwise bromine solution (0.01 mol) at room temperature with stirring for half an hour. The resulting solid was filtered and recrystallized from ethanol as yellowish needles crystals.

Synthesis of 2-[4′-Aminobenzophenone]-(3,5*H*)-1,3-thiazol-4-one (17)

A mixture of **15** (0.01 mol) and ethyl chloroacetate (0.01 mol) added (1 g) of fused sodium acetate; the resulting reaction mixture was refluxed for 3 hr. The cold reaction mixture was poured into cold water. The solid precipitate was filtered and recrystallized from ethanol as buff crystals.

Synthesis of 1-[4′-Benzophenone]-2-mercapto-(3,5*H*)-pyrimidin-4,6-dione (18)

A mixture of thioureido **15** (0.015 mol) and malonic acid (0.015 mol) in CH_3COCl (15 mL) was refluxed for 3 hr. The reaction mixture was cooled, poured into ice and neutralized with K_2CO_3 solution (10%); the deep red solid precipitate was filtered and recrystallized from acetic acid.

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