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Synthesis and Characterization of Some Fluorinated 1, 5 - Benzothiazepines and Pyrazolines

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ABSTRACT

4-Bromo-2-fluorobenzaldehyde 1 when treated with substituted hydroxy acetophenones 2 yields chalcones 3. These chalcones were refluxed with 2-aminothiophenol gave "2-[2-(4-bromo-2-fluorophenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]phenol" 4 and when treated with hydrazine hydrate gave the compound "2-[5-(4-bromo-2-fluorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]phenol" 5. The structures of compounds have been established on the basis of spectral data.

Key words: Fluorinated Chalcones, Benzothiazepines, Pyrazolines.

INTRODUCTION

One of the most important factors in the drug design is that fluorine is much more lipophilic than hydrogen, so incorporating fluorine in the molecule makes it more fat soluble, so it percolates into the membrane more readily and hence fluorinated molecule has a higher bioavailability. Around fifth of all drugs on the market today contain at least one fluorine atom such as Paroxetine, Ezetimibe, Linezolid and Midazolam. Many fluorinated compounds are widely used as antimalarial, antiviral, antipsychotic and antidepressants. Some heterocyclic compounds also act as dyes, pesticides, luminophores and herbicides in nature[1]. Various biological activities associated with chalcones includes antimitotic[2], antiinvasive[3,4], antifungal[5], antituberculosis[6], antileishmanial[7], anti- malarial[8,9], antiinflammatory[10-12], antitumor and antioxidant properties[13]. Their recognized synthetic utility in the preparation of pharmacologically interesting heterocycles as pyrazolines, which includes antiparasitary[14], anti-tumor[15], nitric oxide synthase inhibitors[16] and anti-inflammatory[17] activities.

Benzothiazepines retained the interest of researchers due to the unique structural properties and broad spectrum of biological activities of the compounds[18]. Three possible benzocondensed derivatives of 1,5-benzothiazepines *viz*. 1,4-, 4,1- and 1,5-benzothiazepines[19] are kwown. Benzothiazepines have their role in the treatment of muscle relaxant[20], cardiovascular disorders[21], as

Ca^{2+} channel blockers[22] and inhibitors of HIV-integrase[23]. Pyrazolines reported to have anti-inflammatory[24-26], anti-viral[27], anti-cancer[28-30], anti-diabetic[31] and anti-oxidant[32] properties. Several pyrazoline derivatives found to possess antimicrobial[33] and anti-HIV[34] activities. Some of the pyrazolines were effective in inhibiting the accumulation of prion protein[35], the abnormal protease-resistant form.

Present work

Substituted hydroxy acetophenones **2** on reaction with 4-bromo-2-fluorobenzaldehyde **1** stirred at room temperature for 24 hrs gives respective chalcones **3** which on reaction with 2-amino thiophenol & reflux for 8 hrs gave benzothiazepines **4** and with hydrazine hydrate for 6 hrs which gave pyrazolines **5**.

EXPERIMENTAL

All the recorded melting points were determined in open capillary tubes and are uncorrected. I.R. spectra were recorded on Shimadzu FTIR Spectrophotometer in KBr disc. ^{1}H NMR spectra were recorded on a Bruker Avance II 400 MHz spectrophotometer DMSO-d_6 as a solvent and TMS as an internal standard (chemical shift in δ values). Mass spectra were obtained on a Finnigan mass spectrometer. Purity of the compounds was checked by TLC on silica gel G plates.

Synthesis of Chalcones

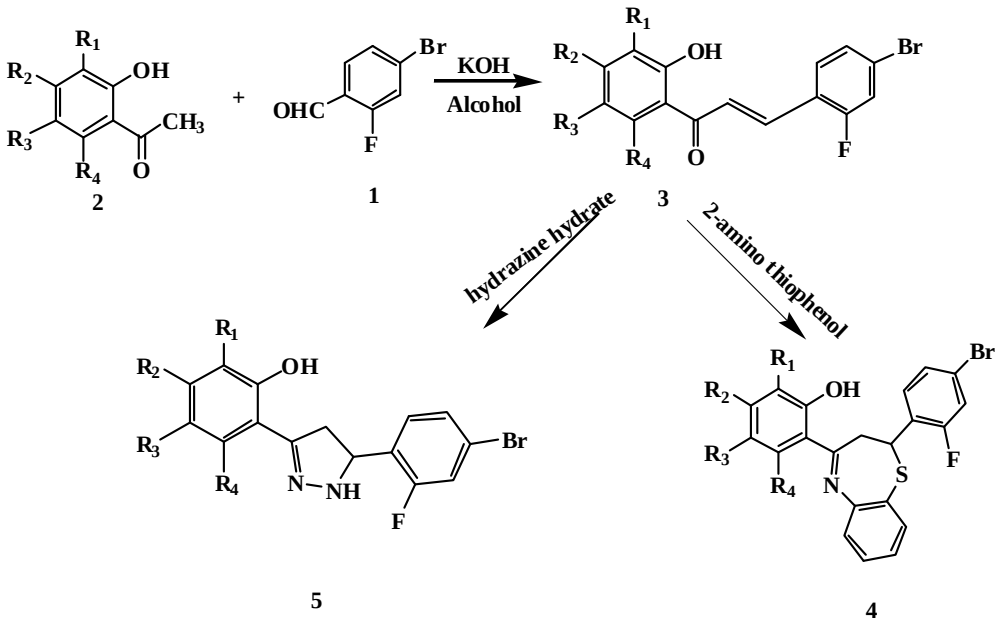
Compound 2 (0.005 mol) & 1 (0.005 mol) were taken in 100 ml RBF with 25 ml ethanol. To this reaction 2 gm of KOH was added & resulting reaction was stirred at room temperature for 24 hrs. Then contents were poured over crushed ice & acidified with conc. HCl, solid thus obtained were separated by filtration & crystallized from ethanol to get compound 3. Their characterization data is in the table-1(**3a-3e**).

Spectral data

3a I.R. (KBr, cm^{-1}): 3059 (Ar =C-H), 2920 (C-H), 1649 (–C=O), 1581 (–C=C), 1211 (–C-F), 1022 (–C-Br); NMR (DMSO/ d_6): δ 2.34 -3.36 (3H, s, CH_3), 6.86-8.12 (6H, m, Ar & =CH protons), 12.30 (1H, s, -OH).

Synthesis of Benzothiazepines

Compound **3** was dissolved in minimum quantity of ethanol. To this, 4-6 drops of 2-aminothiophenol was added and the resulting reaction was refluxed for 4 hrs. Then reaction mixture was acidified by using 2 ml acetic acid and heating was continued for next 4 hrs. After cooling pale yellow crystals **4** were obtained. These were filtered



Scheme 1:

Table 1: Characterization data of synthesized compound

Compound	R_1	R_2	R_3	R_4	M. P. (° C)	Yield (%)
3a	H	H	Br	H	174	65
3b	Cl	H	Cl	H	140	72
3c	H	CH_3	Cl	H	130	67
3d	H	H	CH_3	H	110	62
3e	H	Cl	H	Cl	162	80
4a	H	H	Br	H	170	61
4b	Cl	H	Cl	H	130	63
4c	H	CH_3	Cl	H	175	64
4d	H	H	CH_3	H	180	62
4e	H	Cl	H	Cl	175	62
5a	H	H	Br	H	110	55
5b	Cl	H	Cl	H	190	52
5c	H	CH_3	Cl	H	240	57
5d	H	H	CH_3	H	165	52
5e	H	Cl	H	Cl	182	51

and purified by recrystallization from ethanol. The products obtained were identified with the help of spectral data. Their characterization data is given in the table 1(**4a-4e**).

Spectral data

4b

I.R. (KBr, cm^{-1}):3448 (Ar- O-H), 1598 (C=N), 1552 (C=C), 1207 (–C-F), 1042 (–C-Br); NMR (DMSO/ d_6): δ 1.14 (1H, dd , C-H), 2.99 (1H, dd, C-H), 3.59 (1H, dd, C-H), 7.28-7.66 *(*8H, m, Ar-H), 7.90 (1H, d, Ar-H), 15.50 (1H, OH).

Synthesis of pyrazoline

Compound 3 was taken in 100 ml RBF with 15 ml alcohol. To this reaction mixture 1 ml hydrazine hydrate was added & the contents were heated under reflux for 3 hrs and to this 2 ml acetic acid was added & heating was continued for further 2 hrs. After cooling contents were poured over crushed ice. The solid thus obtained was separated by filtration & crystallized with alcohol to get compounds 5. The products obtained were identified with the help of spectral data. Their characterization data is given in the table 1(5a-5e). Spectral data

5a

I.R.(KBr, cm^{-1}) 3350 (N-H), 2987 (Ar- =C-H), 1602 (–C=N), 1573 (–C=C), 1203 (C-F) 1047 (C-Br); NMR(DMSO/ d_6): δ 3.05 (1H, dd, C-H), 3.67 *(*1H, dd, C-H), 5.07 *(*1H, dd, C-H), 7.25-7.46 *(*6H, m, Ar and NH proton), 8.09 *(* 1H, d, Ar-H) 11.82 (1H, OH).

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