One pot synthesis of substituted benzodiazepine using molecular iodine

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ABSTRACT

The benzodiazepine nucleus is a well studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various biological activities like Sedatives, hypnotic, muscle relaxant, anticonvulsant agent. Molecular iodine catalyst improved procedure of synthesis of various 1,5-Benzodiazepines from orthophenylenediamine (OPD) and various substituted acetophenone at room temperature and excellent isolated yield has been reported. This is a simple, straightforward , high yielding , non-hazardous and inexpensive catalyst.

KEYWORDS: Benzodiazepine, hypnotic, biological activity

INTRODUCTION

Benzodiazepine and its derivatives represent an important class of heterocyclic compounds which produce a wide range of beneficial and pharmacological properties. Derivatives of benzodiazepines are widely used as analgesic, anti depressive, anticonvulsant, anti anxiety, sedative and hypnotic agents (Schutz *et al.*, 1982, Randall *et al.*, 1973). Additionally, 1,5-benzodiazepines are key intermediates for the synthesis of various fused ring systems such as oxadiazolo-, oxazino-, or furano benzodiazepines (Nagaraja *et al*., 2006; Nabih *et al*., 2004). Other than their biological importance, benzodiazepine derivatives are also commercially used as dyes for acrylic fibres (Reddy *et al.*, 2000). Generally these compounds are synthesized by condensation reactions of orthophenylenediamines with ketones, haloketones, chalcones (Jung *et al.*, 1999; Ried *et al*., 1959). A variety of reagents, such as BF_3-etherate, $NaBH_4$, polyphosphoric acid, SiO_2, $MgO/POCl_3$ have been utilized for the condensation reactions (Ricaurte *et al.*, 2004). However all of these methods have problems such as drastic reaction conditions and several side reactions. Use of molecular iodine

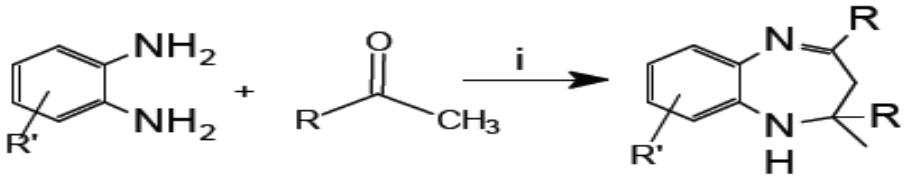
as a catalyst for these condensation reactions have improved procedure for synthesis of 1,5-benzo diazepines at room temperature and excellent isolated yield has been reported (Balakrishna *et al*., 2001, Benjaram *et al.,* 2003). This is a simple, straight forward, high yielding, non hazardous and inexpensive catalyst. Iodine has high tolerance to air as well as moisture and can be easily removed from the reaction mixture by washing with reducing agents. Many of the reations using iodine are associated with mild reaction conditions, grater stereo- and regio-selectivities, short reaction times (Gheorghe *et al.,* 2002). Taking into consideration the wide biological activities of benzodiazepine we have synthesized a series of substituted 1,5-benzodiazepine by keeping our focus on the use of catalytic amount of molecular iodine as iodine has advantages in terms of user and environmental friendliness (Katritzky, 1984).

MATERIALS AND METHODS

All the chemicals were obtained from Shree Sai Chemicals, Solapur. The purity of compounds was determined by thin layer chromatography on silica gel plate. The melting points of synthesized compounds were determined by thiel's melting point apparatus and are uncorrect. ^{1}HNMR spectra were recorded on BRUKER ADVANCE 300 MHz spectrophotometer in $CDCl_3$ with TMS as an internal standard. The chemical shift values are in delta (ppm).

General procedure for synthesis of substituted 1, 5-benzodiazepine (Compounds 1a-1h):

A mixture of substituted orthophenylenediamine (1mmol) and substituted acetophenone (2mmol) were taken in round bottom flask. 2 ml of ethanol was added to the flask and stirred at room temperature for 5-10 min. To this solution 10 mol% iodine was added and the reaction mixture was stirred at room temperature for 5-6 hrs. The reaction is monitored with TLC. After completion of reaction the reaction mixture was diluted with water, the product obtained was filtered, dried, recrystallized with ethanol.



Scheme -1

Reagents and conditions: i) ethanol, 10mol% iodine, rat, 5-6 hrs.

RESULTS AND DISCUSSION

The compounds 1a-1h were synthesized as per the general procedure given in Scheme 1. Use of molecular iodine as a catalyst gave good yield of products with high purity. The physical data of the synthesized compounds were given in Table 1 as below. The reactions were monitored by TLC. The compounds were further characterized by IR & ^{1}H NMR.

Table 1: Physical data of synthesized compounds

Compounds	R	R'	M. P. (^{O}C)	% Yield
1a	3,4-dimethoxy acetophenone	H	156	92
1b	3,4-dimethoxy acetophenone	Cl	162	87
1c	3,4-dimethoxy acetophenone	Fl	160	85
1d	3,4-dimethoxy acetophenone	CH_3	180	90
1e	3,4,5-trimethoxy acetophenone	H	170	94
1f	3,4,5-trimethoxy acetophenone	Cl	178	88
1g	3,4,5-trimethoxy acetophenone	Fl	174	83
1h	3,4,5-trimethoxy acetophenone	CH_3	182	90

Spectral analysis of selected compounds

Compound 1f: IR (KBr) 3333.90 (N-H), 1504 (C=N), 1448 Ar (C=C), 1345 (C-O-C), 2918 cm^{-1} (Ar-H); **^{1}HNMR** (300MHz, CDCl3): 1.80 ppm (s, 3H, -CH_3), 2.82ppm (d, 1H, -CH), 2.85 ppm (d, 1H, -CH), 3.12 ppm (s, 1H, -NH), 3.73ppm (s, 15H, - OCH_3), 3.79 ppm (s, 3H, -OCH_3), 6.78ppm (s, 2H, Ar-H), 7.072ppm (m, 3H, Ar-H), 7.26 ppm (t, 1H, Ar-H) 7.28ppm (t, 1H, Ar-H)

Compound 1g: IR (KBr) 3334.56 (N-H), 1506 (C=N), 1450 Ar(C=C), 1344 (C-O-C), 2916 cm^{-1} (Ar-H); **^{1}HNMR** (300MHz, $CDCl_3$) 1.79 ppm (s, 3H, -CH_3), 2.84 ppm (d, 1H, -CH), 2.87(d, 1H, -CH), 3.15 ppm (s, 1H, -NH), 3.75 (s, 15H, -OCH_3), 3.78 ppm(s, 3H, -OCH_3), 6.72 (s, 2H, Ar-H), 7.11 ppm (m, 3H, Ar-H), 7.16ppm (t, 1H, Ar-H), 7.19 (t, 1H, Ar-H)

Compound 1h: IR (KBr) 3335.10 (N-H), 1506 (C=N), 1446 Ar (C=C), 1343 (C-O-C), 2921 cm^{-1} (Ar-H); **^{1}HNMR** (300MHz, $CDCl_3$): 1.82 ppm (s, 3H, -CH_3), 2.84 ppm (d, 1H, -CH), 2.85 ppm (d, 1H, -CH), 3.14 ppm (s, 1H, -NH), 3.75 ppm (s, 15H, - OCH_3), 3.81 ppm (s, 3H, -OCH_3), 6.77 ppm (s, 2H, Ar-H), 7.08 ppm (m, 3H, Ar-H), 7.28 ppm (t, 1H, Ar-H) 7.30 ppm (t, 1H, Ar-H)

CONCLUSION

The results showed that the use of catalytic amount of molecular iodine in synthesis of benzodiazepine greatly reduced the time required for the reaction to complete. The yields obtained were good and the products were of high purity. The catalyst is eco friendly and hence provide route for green synthesis of substituted benzodiazepines.

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