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Unexpected Synthesis Of Benzalazines

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INTRODUCTION

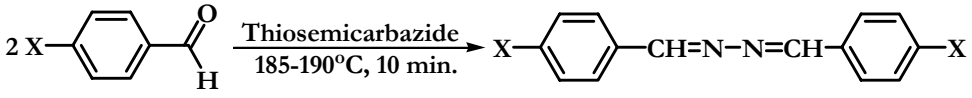
Benzalazines are widely used reagents in organic synthesis and a variety of reactions using benzalazines are employed to prepare hosts of heterocyclic compounds such as fuctionalized 2,3-dihydropyrroles[1], 1,2,4-triazoles and 1,2,4-triazines[2]. Several synthetic procedures have been developed to access benzalazines including reaction of hydrazine hydrate with substituted benzaldehydes[3] and condensation of the required benzaldehyde(2mol) and hydrazine(1mol) which is liberated in situ from its salt by addition of ammonia or potassium acetate[4,5]. Other methods involve treatment of benzaldehydes with hydrazine hydrate either in acetic acid[6] or polyphosphoric acid (PPA)[7], air oxidation of ammonium salts and benzylhydrazones in DMSO[8] and oxidation of ammonia with hydrogen peroxide in the presence of benzaldehydes[9]. Recently a modified method employing anhydrous sodium acetate and calcium chloride under microwave irradiation in dry condition has been reported[10].

However many of these procedures have significant drawbacks such as low yields of products, long reaction times and difficulties in work-up. Thus the development of more efficient procedure for the synthesis of benzalazines is still needed.

As part of a continuing effort in our laboratory to study the thermal behavior of thiosemicarbazide in the presence of both nucleophilic and electrophilic reagents[11] we treated benzaldehyde with thiosemicarbazide in an oil bath for a short period of time. To our surprise we obtained 1,2-bis[1-phenyl methylidene] hydrazine in 91% yield(SCHEME 1). Literature indicates that benzalazines are accessible through thermolysis of the corresponding semi-carbazones via the proposed N-substituted isocyanate as the reactive intermediate[12]. On this basis our reaction may proceed via a reactive isothiocyanate intermediate which is eventually converted to its benzalazine analogue. We have not isolated either intermediate.

Similar treatment of various benzaldehydes with thiosemicarbazide gave the corresponding substituted benzalazines in high yields. Overally, the reaction is very clean, rapid, efficient and the experimental procedure is very simple. The high yield transformation did not form any significant amount of undesirable side products. The results shown in TABLE 1

Short Communication



X= H, Me, OMe, OEt, Cl, Br, NO_2, $N(Me)_2$

SCHEME 1

TABLE 1: Melting points and yields for benzalazines

Entry	X	Yield[a] %	mp(°C)	Lit.mp(°C)
1	H	91	92	92-93[13]
2	Me	91	156	157[3]
3	OMe	92	169	170[5]
4	OEt	94	172	172-173[15]
5	Cl	93	202	201-201.5[14]
6	Br	94	222	223.5-224.5[16]
7	NO_2	96	308	308[11]
8	$N(Me)_2$	95	255	253[7]

[a]Isolated yields

clearly indicate the scope and generality of the reaction with respect to various aromatic aldehydes.

EXPERIMENTAL

The melting points were recorded on an Electrothermal type 9100 melting point apparatus. The FT-IR Spectra were obtained on a 4300 Shimadzu spectrometers as KBr disks. The ^{1}HNMR spectra were recorded on Bruker AM100 spectrometer in $CDCl_3$ solution. The mass spectra were scanned on a Varian CH-7 instrument at 70eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer.

Preparation of benzalazines

To the melted thiosemicarbazide(0.05mol) at 185-190°C in an oil bath was added benzaldehyde or its derivatives(0.01mol.) at once. After ten minutes, the reaction mixture was cooled and the resulting solid was extracted with cyclohexane(3×30ml). Evaporation of the solvent in vaccu furnished the corresponding benzalazine in high yield(>90%) with no need for further purification.

In conclusion, we have demonstrated a simple and efficient procedure for the synthesis of benzalazines via thermal condensation of benzaldehydes with thiosemicarbazide. The significant features of this method include: (a) operational simplicity, (b) high yields of products and (c) short reaction time.

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