NEW METHOD FOR PREPARATION OF SUBSTITUTED PHENAZINES UTILIZING REDOX REACTION

Akira SUGIMOTO[1*], Haichen JIN[1], Kaku UEHARA[1], Tomohiro ADACHI[2], and Hiroo INOUE[1]

[1]Department of Applied Chemistry, College of Engineering, University of Osaka Prefecture, Sakai, Osaka 593, JAPAN

[2]Department of Chemistry, Faculty of Integrated Arts and Sciences, University of Osaka Prefecture, Sakai, Osaka 593, JAPAN

ABSTRACT:

1-Fomyl-, 2-formyl- and 2,7-dibenzoyl-phenazines were prepared from phenazine through the formation of the corresponding substituted 5,10-dimethyl-5,10-dihydrophenazines, followed by demethylation with hydrobromic acid in dimethyl sulfoxide.

INTRODUCTION

As phenazine is a π-electron deficient hetero-aromatic compound, it is difficult to introduce electrophiles into the benzene ring (1). Therefore, the synthesis of the substituted phenazines has been generally carried out by cyclization of the suitable compounds containing substituents (2) and by conversion of substituents (3). We now report the new method for preparing the substituted phenazines, 1-formyl-, 2-formyl- and 2,7-dibenzoyl-phenazine, 3a - c, from phenazine by the electrophilic substitution of 5,10-dihydro-5,10-dimethylphenazine, followed by demethylation with hydrobromic acid in dimethyl sulfoxide (DMSO).

EXPERIMENTAL

Melting points were determined on a Yanaco micro-melting point apparatus and are given uncorrected. NMR spectra were recorded on a JNM-GX270 (270 MHz) type spectrometer using tetramethylsilane as internal standard. Chromatography was carried out on silica gel.

Procedure for synthesis of compounds 1 and 2a - e

All reactions were performed under argon atmosphere.

Procedure for compound 1

To a solution of phenazine (1.1 mmol) in ethanol (50 ml) was addd successively sodium dithionite (20 g) and water (1.5 l) under vigorous stirring. After cooling, the solids were filtered off and dried under vacuum to give 5,10-dihydro-5,10-dimethylphenazine almost quantitatively. To a solution of 5,10-dihydrophenazine (21.8 mmol) in 1,2-dimethoxyethane (90 ml) was added dropwise n-butyl-lithium (44.4 mmol in 15% hexane solution), subsequently methyl iodide (66.6 mmol). The reaction mixture was treated with a mixture of aq. sodium dithionite solution and benzene. The benzene layer was

separated and dried with anhydrous sodium sulfate. After evaporation of solvent, the residue was purified by chromatography with toluene to give 1.

Procedure for compounds 2a and 2b.

To a mixture of phosphorous oxychloride (27.4 mmol) and N,N-dimethylformamide (55 mmol) was added a solution of 3a (13.7 mmol) in dichloromethane (20 ml). After heating at reflux for 2 h, the mixture was poured into a large amount of a cold aq. solution of sodium acetate and the solids deposited were filtered off and purified by chromatography with toluene to give 2a and 2b.

Procedure for compound 2c

To a suspension of anhydrous aluminum chloride (4.49 mmol) in carbon tetrachloride (15 ml) was added dropwise benzoyl chloride (4.25 mmol) at room temperature. To the refluxing mixture was added a solution of 1 (2.38 mmol) in carbon tetrachloride (20 ml) with stirring and the mixture was heated at reflux for 1.5 h. After cooling, the reaction mixture was poured into a large amount of ice-water and made alkaline with aq. solution of sodium carbonate. After extraction with methane dichloride, the extract was dried over sodium sulfate and evaporated to dryness. The residue was purified by chromatography with methane dichloride to give 2c.

Procedure for compounds 2d and 2e

Compounds 2d and 2e were synthesized by the procedure being similar to that in the case of 2c.

General procedure for the demethylation reaction

To a solution of 2a - e (5 mmol) in DMSO (15 ml) was added hydrobromic acid (0.6 ml of 47 % aq. solution) at 80 - 90°C under stirring. After stirring at 80 - 90°C for 1.5 h, the reaction mixture was neutralized with ammonium hydroxde and extracted with benzene. The extract was dried over sodium sulfate and evaporated to dryness. The residue was purified by chromatography with toluene. The structure of 3c was established by X-ray crystal structure analysis (Fig.1).

X-ray crystal structure analysis

X-ray diffraction data were collected by using Rigaku AFC5R diffractometer with graphite monochromated Mo-Kα radiation (λ=0.71069A) and a 18 kw rotating anode generator. Cell dimensions were obtained by least-square fitting from 25 high angle reflections. All computations for the structure determination were carried out on VAX station 3100 using crystallographic program package TEXSAN (4).

Crystal data for 3c: $C_{26}H_{16}N_2O_2$; monoclinic; space group $P2_1/a$ (No. 14), a=8.114(1), b=11.214(2), c=10.259(1)Å, β=95.61(1)°, U=929.0(2)$Å^3$; D_c=1.388gcm^{-3}, Z=2, μ=0.83 cm^{-1}.

A total of 2415 independent reflections were collected. The structure was solved by direct method and was then refined by full-matrix least-square procedure. Anisotropic thermal parameters were adopted for non-hydrogen atoms. The final R (Rw) value converged to 0.043 (0.034).

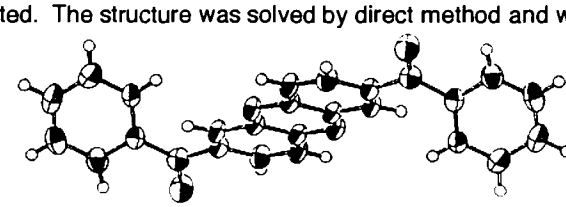
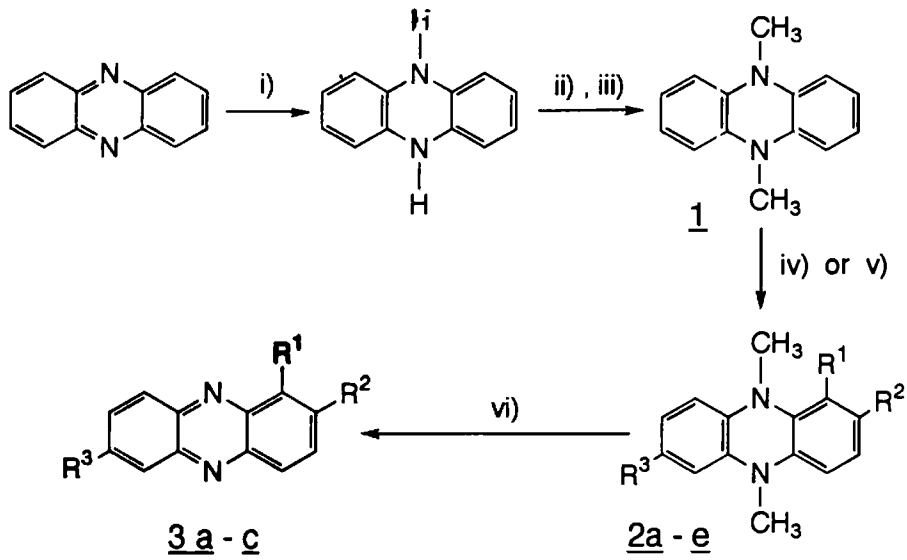


Fig. 1. ORTEP drawing of compound 3c

RESULTS AND DISCUSSION

Synthetic pathways are summarized in Scheme 1.



a : R^1 = CHO, R^2 = R^3 = H d : R^1 = R^3 = H, R^2 = $COCH_3$

b : R^1 = R^3 = H, R^2 = CHO e : R^1 = H, R^2 = R^3 = $COCH_3$

c : R^1 = H, R^2 = R^3 = COPh

i) $Na_2S_2O_4$, H_2O; ii) BuLi; iii) CH_3I; iv) $HCO(CH_3)_2$, $POCl_3$;
v) PhCOCl or CH_3COCl, $AlCl_3$; vi) HBr, CH_3SOCH_3

Scheme 1

The reduction of phenazine to 5,10-dihydrophenazine, followed by methylation, made possible the electrophilic substitution of the benzene ring (Table 1). The methylation was neccessary for subsequent substitution reaction, since 5,10-dihydrophenazine was oxidized easily by air. The formylation of 1 with Vilsmeier reagent gave the 2-substituted dihydrophenazines, 2b, in high yield together with 2a. The acylation of 1 gave 2,7-di-substituted dihydrophenazines, 2c and 2e, in moderate yields.

The treatment of 1 with hydrobromic acid in DMSO was found to give phenazine in 78% yield. This reaction is explained to proceed via the formation of the HBr salt of 1, followed by demethylation to give the HBr salt of 5,10-dihydrophenazine which is oxdized by air on treatment with ammonium hydroxide. The demethylation reaction of 2a - c under similar conditions gave the corresponding phenazines, 3a - c, in moderate yields (Table 1), although the reaction of 2d and 2e was unsuccessful because of Aldol condensation.

The melting points, yields, and spectral data of 1, 2a - e, and 3a - c are summarized in Table 1.

Table 1: Melting points, yields, and spectral data of 1, 2a - e, and 3a - c

Comp.*	R^1	R^2	R^3	Mp (°C)	Yield (%)	IR (CO) (cm^{-1})	CH_3	^{1}HNMR** ArH and CHO
1	H	H	H	151-152***	92	-	2.57	6.20-6.24(4H), 6.73-6.78(4H)
2a	CHO	H	H	83 - 84****	8	1665	2.94, 3.26,	6.35-6.38(2H), 6.52-6.55(1H), 9.94(1H, CHO) 6.69-6.78(3H), 7.04-7.08(1H)
2b	H	CHO	H	106-107****	85	1685	3.07	6.37-7.26(7H), 9.66(1H, CHO)
2c	H	COPh	COPh	269-270	65	1632	3.13	6.35-6.38(2H), 6.98-7.02(2H),7.17-7.20(2H), 7.43-7.58(6H), 7.71-7.74(4H)
2d	H	COMe	H	99.5-100	8	1661	2.48, 3.06(d),	6.31-6.45(3H), 6.70-6.81(2H), 6.93-6.94(1H), 7.33-7.36(1H)
2e	H	COMe	COMe	227-228	63	1660	2.48, 3.09,	6.34-6.37(2H), 6.97-6.99(2H), 7.34-7.39(2H)
3a	CHO	H	H	176-177*****	54	1693		7.88-8.01(3H), 8.25-8.35(2H), 8.47 (2H), 11.92(1H, CHO)
3b	H	CHO	H	184-184.5*****	60	1697		7.91-7.95(2H), 8.28-8.37(4H), 8.74(1H), 10.33(1H, CHO)
3c	H	COPh	COPh	260-261	61	1650		7.57-7.69(6H), 7.94-7.96(4H), 8.36-8.37(4H), 8.60-8.65(2H)

* Analyses agree within 0.4% of the theoretical values.

** C_6D_6 for 2 and $CDCl_3$ for 3. Tetramethylsilane as internal standard.

*** A. Sugimoto, T. Kotani, J. Tsujimoto and S. Yoneda, J. Heterocycl. Chem. **26**, 435 (1989)

**** M. G. Khristiansen, Ya. A. Il'chenko and Yu. S. Rozum, Dopov. Akad. Nauk.Rsr, Ser. B, **32**, 829 (1970); Chem. Abst. **74**, 99989s (1971)

***** Lit. 3.

The above results provide the new method for introducing the substituents into the benzene ring of phenazine by utilizing the reactivity of 1 which undergoes substitution and demethylation reaction.

REFERENCES

(1) G. A. Swan and D. G. I. Felton, Phenazines, Interscience Publishers, 1957; A. R. Katritzky and C. W. Rees (Ed), Comprehensive Heterocyclic Chemistry, Pergamon Press, Oxford, **3**, 1984, pp.157

(2) A. Wohl and W. Aue, Chem. Ber. **34**, 2442 (1901) and Ref. (1)

(3) Yu. S. Rozum, Zhur. Obshchei. Khim. **25**, 611 (1955)

(4) TEXSAN - TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985)

Received September 29, 1994