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Vicarious nucleophilic substitution in enamine derivatives of 1-hydroxynaphthalene-2,4-dicarbaldehyde☆

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Abstract—The reaction of aromatic amines with highly stable Schiff base enamines formed from an alkyl amine and 1-hydroxynaphthalene-2,4-dicarbaldehyde resulted in nucleophilic substitution of the alkyl amine with the aromatic amine in ethyl alcohol at room temperature within 1–2 min. This reactivity, regioselectivity and formation of stable derivatives are due to extra stabilization through extended conjugation in these systems.

Schiff bases are a very interesting group of compounds characterized by their important role in biological systems.[1–6] For example, in rodopsine, halorodopsine and bacteriorhodopsine, retinal molecules are connected to a peptide through the NH_2 group of a lysine residue forming a Schiff's base. Furthermore, Schiff bases are observed in various enzymes such as tryptophan synthase, transaminases and transketolases.

In continuation of our research on the synthesis of biologically active compounds, we have recently synthesized a series of novel Schiff bases from two aromatic dialdehydes, in which the reactions were regioselective and the products existed in the keto-enamine form, in which the aromaticity of the relevant ring was disrupted.[7] We were curious to determine the reactivity of aromatic amines and whether they existed in imine or enamine form. We thought that the free aldehyde at position 4 would react with an aromatic amine and envisaged a final product which would exist in the imine form thereby resulting in a product having both an imine and enamine, for example, **4** (Scheme 1). The results of our investigations form the subject matter of this Letter.

It is worth mentioning that starting material **1** formed by condensation of an alkyl amine with a dialdehyde was highly stable and our efforts to bring the free aldehyde group into reaction failed both with increasing molar ratio of the alkyl amine and also by increasing the reaction temperature to reflux. However, when we treated **1** with *p*-toluidine, product **3c** was formed almost instantaneously. The ESI-mass spectrum of **3c** gave a molecular ion at *m*/*z* 289. The ^{1}H NMR of the product in addition to other signals showed a signal at δ 9.98 for the aldehyde. The product existed in the keto-enamine form as the NH proton (which resonated at δ 13.1 in the case of simple alkyl amines) appeared at δ 15.1. This increase in chemical shift can be ascribed partly to a slightly stronger hydrogen bond and partly to ring current effects. The NH proton gave a cross peak with the enamine proton at δ 8.38 in the COSY spectrum. Inspection of the HMBC spectrum showed that the enamine proton at δ 8.38 gave long range correlations with the signals at δ 179.6 (CO), δ 107.9 (C-2), δ 144.4 (C-3) and δ 136.4 (N–C_6H_5). Also, HMBC correlations (Fig. 1) of the formyl proton at δ 9.98 with the carbons at δ 144.4, δ 134.8, δ 131.2 and δ 120.5 supported the presence of the free formyl group located at C-4. Final analysis of all the spectral data led to structure **3c** in which the alkyl amine had been substituted with the aromatic amine (Scheme 1).

Makosza and co-workers have reported the vicarious nucleophilic substitution of hydrogen in electrophilic aldimines and thereby synthesized enamines substituted with electron withdrawing groups.[8]

Keywords: Schiff bases; Imine; Enamine; NMR spectroscopy; Regioselectivity; 1-Hydroxynaphthalene-2,4-dicarbaldehyde.

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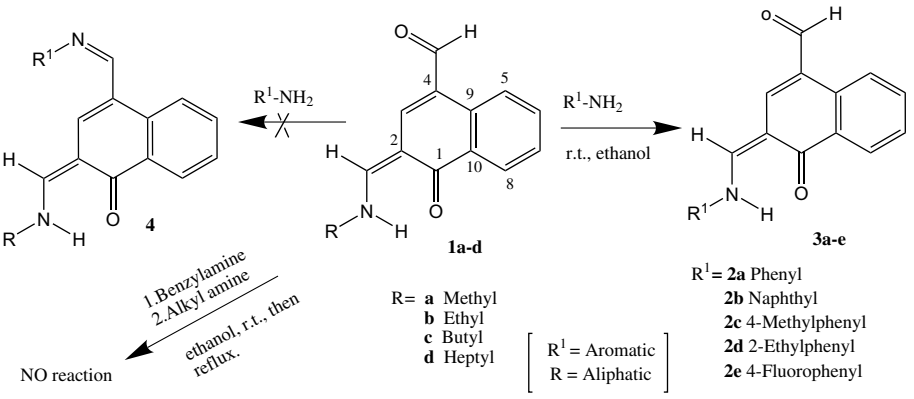

Scheme 1. Synthesis of aromatic enamine derivatives of 1-hydroxynaphthalene-2,4-dicarbaldehyde.

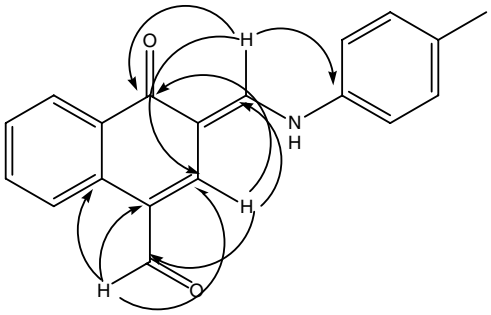

Figure 1. Selected ^{1}H–^{13}C HMBC correlations of **3c** in $CDCl_3$.

To the best of our knowledge, this is the first example of nucleophilic substitution of stable alkyl amines with aromatic amines in naphthalene based systems. The driving force for this nucleophilic substitution of a stronger base by a weaker base can be explained by the fact that the structures formed are stabilized by extended conjugation in the aromatic amine system. As expected, the reaction did not take place with benzylamine and the reactants remained intact (Scheme 1). Detailed mechanistic studies of this reaction will be reported in due course.

All the aromatic amines **2a**–**e** underwent nucleophilic substitution[9] with methylamine Schiff base enamine **1a**. The reaction also took place with ethyl, butyl and *n*-heptyl amines in comparable times and yields (Table 1).

The reaction of the starting material, aromatic dialdehyde with *p*-toluidine **2c** also instantaneously resulted in the same product **3c**. All new compounds were identified by ^{1}H NMR, ^{13}C NMR, 2D NMR (COSY, HSQC and HMBC) and by mass spectroscopy.[10]

In summary, we have described nucleophilic substitution in alkyl enamine derivatives of 1-hydroxynaphthalene-2,4-dicarbaldehyde. This route should provide a simple and versatile entry to a wide variety of polycyclic systems, and we are currently pursuing these ideas.

Table 1. Nucleophilic substitution of alkyl enamines (**1a**, entries 1–5, **1b**, entries 6–10, **1c**, entries 11–15 and **1d**, entries 16–20) with various aromatic amines **2a**–**e**

Entry	Ar–NH_2	Time (s)	Isolated yield (%)	Mp (°C)
1	**2a**	56	66	192
2	**2b**	72	60	251
3	**2c**	65	75	186
4	**2d**	75	68	183
5	**2e**	96	62	162
6	**2a**	88	61	192
7	**2b**	94	66	251
8	**2c**	86	72	186
9	**2d**	77	66	183
10	**2e**	110	61	162
11	**2a**	58	70	192
12	**2b**	68	64	251
13	**2c**	67	73	186
14	**2d**	88	58	183
15	**2e**	94	60	162
16	**2a**	68	62	192
17	**2b**	96	63	251
18	**2c**	98	68	186
19	**2d**	88	60	183
20	**2e**	96	58	162

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Supplementary data

Supplementary data (Spectral data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.03.007.

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9. *Typical procedure*: To aliphatic enamine **1a** (2 mmol) was added 4-methylaniline (4 mmol) in absolute ethanol (10 ml) and the reaction mixture was stirred at room temperature for 1–2 min. The solid formed was filtered and washed with water. The crude product was purified by column chromatography over silica gel to provide aromatic enamine **3c** in good yield.
10. *Selected physical data*: Compound **3c** mp 186 °C; IR (KBr): 3416, 2922, 2815, 1595, 1443, 1353 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 15.11 (s, 1H), 9.98 (s, 1H), 9.2 (d, $J = 8.04$ Hz, 1H), 8.51 (d, $J = 8.3$ Hz, 1H), 8.38 (d, $J = 10.9$ Hz, 1H), 7.76–7.71 (m, 1H), 7.64 (s, 1H), 7.58–7.53 (m, 1H), 7.30–7.27 (m, 4H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.65, 179.61, 152.95, 144.42, 136.42, 134.80, 132.61, 131.23, 129.45, 128.68, 125.35, 124.54, 124.18, 120.59, 117.38, 107.92, 19.80; ESI-MS: 290 (M+1).