Hydrolysis of Schiff Bases Promoted by UV Light

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The first hydrolysis of Schiff base under 365 nm UV light is reported. The reaction was affected markedly by the solvent used. It has been successfully applied to the synthesis of compound **2c** which is a useful antitumor agent.

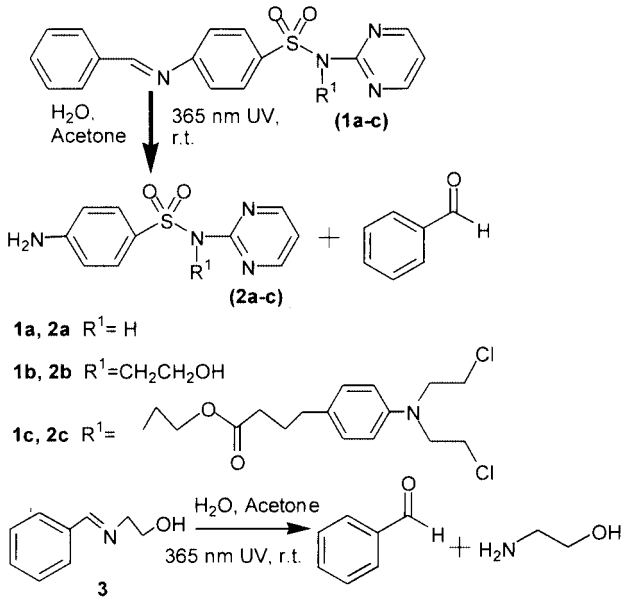
Schiff bases have been widely used as protective group of amino group in organic synthesis.[1–4] The hydrolysis of Schiff bases had been carefully investigated by Jencks.[5,6] In most cases, the cleavage reaction was carried out in acid or alkaline conditions. In some cases, the Schiff base can be cleaved by catalytic hydrogenation.[2] However, these methods may suffer from serious side reactions when multiple functionality is present elsewhere in the substrate molecule. Thus it is meaningful to develop new method for the convenient cleavage of Schiff bases.

In our continuous effort to synthesize new antitumor agents, Schiff base was selected as protective group of the aromatic amine of sulfadiazine. It was noted that compound **1a** was gradually cleaved in the presence of sunlight when acetone was used as solvent. Further investigation showed that the cleavage of the Schiff base of **1a** was due to the hydrolysis reaction, which was supported by the fact that no cleavage reaction can be observed in the absence of water. Furthermore, the reaction was accelerated by the addition of water to acetone. The reaction route is illustrated in Scheme 1 and the results are summarized in Table 1.

Table 1. Hydrolysis of Schiff bases

Entry	Substrate	Conditions[a]	Solvent	Yield /%[b]
1	**1a**	A	acetone	85
2	**1a**	B	acetone	0[c]
3	**1a**	C	acetone	98[d]
4	**1a**	D	acetone	0[c]
5	**1b**	C	acetone	97[d]
6	**1c**	C	acetone	99[d]
7	**3**	C	acetone	92[d]
8	**1b**	C	THF	31
9	**1c**	C	THF	25
10	**1c**	E	THF	94[d]
11	**1b**	E	DMF	0[c]
12	**1c**	E	DMF	0[c]

[a]All the reactions were conducted under nitrogen atmosphere. Condition A: H_2O, sunlight, r.t., 15 days; Condition B: anhydrous acetone, sunlight, r.t., 15 days; Condition C: H_2O, 365 nm UV light, r.t., 40 min; Condition D: H_2O, in dark, r.t., 3 days; Condition E: H_2O, 365 nm UV light, r.t., 4 h. [b]isolated yield. [c]TLC indicated that there was no reaction. [d]TLC indicated that substrate was completely hydrolyzed.



Scheme 1.

The comparison of Entry 1 with Entry 4 suggests that sunlight is a promoter for the hydrolysis since the reaction in the dark is too slow to be detected. This can be further substantiated by the comparison of Entry 4 with Entry 3 that the reaction under UV light was much more efficient. Therefore, it can be concluded that the hydrolysis of **1a**, in fact, was promoted by UV light.

The hydrolysis of the Schiff bases was affected markedly by the solvents used. As shown in Table 1, **1b** and **1c** were completely hydrolyzed in acetone solution within 40 min (Entries 5 and 6) while in THF solution only 31% and 25% yields were obtained with other conditions unchanged (Entries 8 and 9). However, high yield can be achieved if the reaction time is long enough (Entry 10). But, when DMF was used as solvent the hydrolysis reaction did not occur at all, even the reaction time was long enough (Entries 11 and 12). It seems that the Schiff base is stabilized by DMF though the mechanism is still unclear.

Accordingly, Condition C has been chosen as the preferable reaction condition and acetone is taken as solvent for the hydrolysis of the Schiff bases. It has been successfully applied to the hydrolysis of **1a**, **lb**, **lc** and **3** as listed in Entries 3, 5, 6 and 7, respectively.[7,8] The advantage of this deprotection method has been fully demonstrated in the synthesis of **2c**, since **2c**, a potent antitumor agent, is sensitive to acid or alkaline conditions and is unstable at relatively high temperature.

In conclusion, we have developed a new efficient method for the hydrolysis of Schiff bases by the employment of 365 nm UV light. The application of this method to the synthesis of **2c** has been successful. Further research focusing on the mechanism of this reaction is in progress.

References and Notes

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7 Typical procedure for the hydrolysis of the Schiff bases under UV light: To a solution of **1c** (3 g) in acetone (60 mL) was added distilled water (5 mL). With nitrogen gas slightly bubbling through, the reaction solution was irradiated by a 300 W high-pressure mercury lamp for 40 min at r.t. Cupric sulfate aqueous solution was used as the photofilter to obtain 365 nm monochromatic light. After the removal of the solvent, the crude product was washed with ethyl ether to remove benzaldehyde, then the residue was dried at vacuum. **2c** was obtained as white solid in yield of 99%.
8 Satisfactory analyses (within ±0.4%) were obtained for all new compounds. Selected data for **1b:** mp: 186–187 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.77 (t, 2H, CH_2CH$_2$OH), 4.15 (t, 2H, CH$_2$CH_2OH), 5.06 (t, 1H, CH$_2$CH$_2$O*H*), 6.84 (dd, 1H, pyrimidinyl), 7.30 (d, 2H, phenyl), 7.58 (m, 3H, phenyl), 7.89 (d, 2H, phenyl), 7.95 (dd, 2H, phenyl), 8.32 (dd, 1H, pyrimidyl), 8.61 (dd, 1H, pyrimidyl), 8.63 (s, 1H, ArC*H*=N); MS (EI) *m/z* (RI) 382 (M^+, 6), 348 (19), 279 (46), 260 (100), 244 (38), 196 (82), 180 (85), 152 (55), 109 (31). **2b:** mp: 224–226 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.73 (t, 2H, *J* = 4.5 Hz, CH_2CH$_2$OH), 4.07 (t, 2H, *J* = 4.5 Hz, CH$_2$CH_2OH), 5.02 (t, 1H, *J* = 5.4 Hz, CH$_2$CH$_2$O*H*), 5.66 (br s, 2H, NH$_2$), 6.51 (d, 2H, *J* = 8.7 Hz, phenyl), 6.73 (dd, 1H, *J* = 2.4 Hz, *J* = 4.2 Hz, pyrimidinyl), 7.51 (d, 2H, *J* = 8.7 Hz, phenyl), 8.23 (dd, 1H, *J* = 2.4 Hz, *J* = 4.2 Hz, pyrimidyl), 8.58 (q, 1H, *J* = 2.4 Hz, pyrimidyl); MS (EI) *m/z* (RI) 295 ($[M+H]^+$, 15), 172 (60), 156 (100), 108 (29), 108 (83), 92 (81), 65 (68). **1c:** mp:141–142 °C; ^{1}H NMR (300 MHz, Acetone-d_6) δ 1.83 (m, 2H, CH$_2$CH_2CH$_2$), 2.32 (t, 2H, *J* = 7.2 Hz, O=CCH_2CH$_2$CH$_2$), 2.50 (t, 2H, *J* = 7.2 Hz, CH$_2$CH$_2$CH_2Ph), 3.80 (m, 8H, N(CH_2CH_2Cl)$_2$), 4.51 (t, 2H, *J* = 2.1 Hz, NCH_2CH$_2$O), 4.59 (t, 2H, *J* = 2.1 Hz, NCH$_2$CH_2O), 6.74 (d, 2H, *J* = 8.7 Hz, phenyl), 6.79 (dd, 1H, *J* = 2.4 Hz, *J* = 4.2 Hz, pyrimidinyl), 7.04 (d, 2H, *J* = 8.7 Hz, phenyl), 7.32 (d, 2H, *J* = 8.7 Hz, phenyl), 7.59 (m, 3H, phenyl), 8.02 (d, 2H, *J* = 3 Hz, phenyl), 8.07 (d, 2H, *J* = 3 Hz, phenyl), 8.38 (dd, 1H, *J* = 2.4 Hz, *J* = 4.2 Hz, pyrimidyl), 8.60 (s, 1H, ArC*H*=NAr), 8.62 (q, 1H, *J* = 2.4 Hz, pyrimidyl). **2c:** mp: 97–98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.81 (m, 2H, CH$_2$CH_2CH$_2$), 2.23 (t, 2H, *J* = 7.2 Hz, O=CCH_2CH$_2$CH$_2$), 2.53 (t, 2H, *J* = 7.2 Hz, CH$_2$CH$_2$CH_2Ph), 3.60 (t, 4H, *J* = 6.0 Hz, N(CH$_2$CH_2Cl)$_2$), 3.70 (t, 4H, *J* = 6.0 Hz, N(CH_2CH$_2$Cl)$_2$), 4.25 (t, 2H, *J* = 4.5 Hz, NCH_2CH$_2$O), 4.43 (t, 2H, *J* = 4.5 Hz, NCH$_2$CH_2O), 5.64 (br s, 2H, NH$_2$), 6.46 (dd, 1H, *J* = 2.4 Hz, *J* = 4.2 Hz, pyrimidinyl), 6.64 (dd, 4H, *J* = 8.4 Hz, *J* = 2.4 Hz, phenyl), 7.00(d, 2H, *J* = 6.9 Hz, phenyl), 7.66 (dd, 1H, *J* = 2.4 Hz, *J* = 4.2 Hz, pyrimidyl),7.81 (d, 2H, *J* = 6.9 Hz, phenyl), 8.58 (q, 1H, *J* = 2.4 Hz, pyrimidyl).