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An improved synthesis of isonitrosoacetanilides

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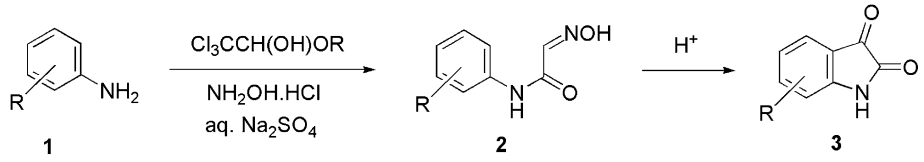
Abstract—A novel two-step synthesis of isonitrosoacetanilides [2-(hydroxyimino)-*N*-phenylacetamides] has been developed, involving the initial acylation of aniline derivatives with 2,2-diacetoxyacetyl chloride, followed by reaction with hydroxylamine hydrochloride. The method works equally well with a variety of different aniline derivatives, including those with poor aqueous solubility and those containing electron rich *ortho*-substituents, neither of which react well under traditional conditions.

The Sandmeyer isonitrosoacetanilide method[1,2] is the most frequently used route to isatins **3** (Scheme 1) and its use for this purpose has been well reviewed.[3–6] Traditionally the method involves treating a substituted aniline with chloral hydrate and hydroxylamine hydrochloride (or other hydroxylamine salt), in an aqueous sodium sulfate medium.[2] Recent modifications include the use of ethanol as a co-solvent,[7] microwave irradiation,[8] and the use of the ethyl hemiacetal of chloral, 2,2,2-trichloro-1-ethoxyethanol, as an alternative chloral source,[9,10] although the other components remained unchanged.

The synthesis of isonitrosoacetanilides **2** by the Sandmeyer method is less efficient with aniline derivatives having poor solubility in the aqueous sodium sulfate medium, but more importantly, it fails to work well with anilines that contain electron rich *ortho*-substituents.[11,12] In fact, the only currently viable route to isonitrosoacetanilides with electron rich *ortho*-substituents requires a five-step procedure, which involves the intermediacy of nitrone intermediates.[11]

We have developed a two-step synthesis of isonitrosoacetanilides **2** that involves the simple acylation of anilines **1** with 2,2-diacetoxyacetyl chloride,[13,14] followed by reaction of the resulting 2,2-diacetoxyacetanilide **4** with hydroxylamine hydrochloride in refluxing aqueous ethanol (Scheme 2).[15] Hydrolysis of the diacetates **4** to the aldehyde occurs in situ, eliminating the need to perform a separate hydrolysis step. A similar transformation has previously been reported using 2-chloro-2-ethoxyacetyl chloride as the acylating species,[16] but the poor availability[17,18] of this reagent compared to 2,2-diacetoxyacetyl chloride makes the present procedure much more viable for larger scale use. We also investigated the use of 2,2-diethoxyacetanilides, 2,2-bis(4-chlorophenoxy)acetanilides, and 2,2-dichloroacetanilides as a source of the isonitrosoacetanilides **2**, and although successful reaction with hydroxylamine hydrochloride



Scheme 1. Sandmeyer isatin synthesis.

Keywords: Aniline; Isatin; Isonitrosoacetanilide.
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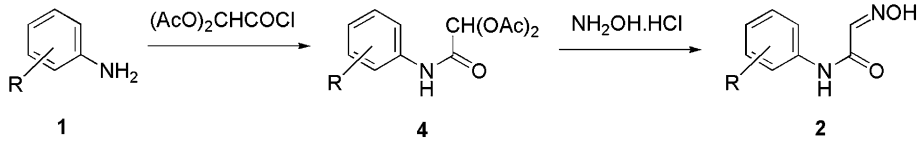
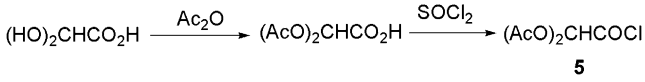


Scheme 2. Two-step synthesis of isonitrosoacetanilides.



Scheme 3. Synthesis of 2,2-diacetoxyacetyl chloride (**5**).

did occur in the first case, we found the reaction involving the diacyloxy species **4** to be much more facile.

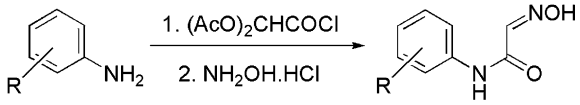
2,2-Diacetoxyacetyl chloride (**5**) is readily prepared by the literature procedure,[13] which involves acylation of glyoxylic acid monohydrate with acetic anhydride, followed by reaction with thionyl chloride (Scheme 3). In addition, we found that 50% aqueous glyoxylic acid could equally be used as the starting material,[14] provided additional acetic anhydride was employed to neutralize the extra water. Following removal of excess thionyl chloride and other volatiles, clean acid chloride **5** was obtained by vacuum distillation.

For the acylation reaction between the acid chloride **5** and aniline derivatives **1**, we investigated a number of different bases, but found that $KHCO_3$ offered the best compromise in terms of yield and ease of use.[15] Simple filtration to remove the inorganic base, followed by removal of solvent, gave the crude diacetates **4**, which could be purified by recrystallization or chromatography on silica, but normally were treated directly with hydroxylamine hydrochloride in refluxing ethanol to furnish the isonitrosoacetanilides **2**. The products were usually sufficiently pure for direct conversion to isatins, but when further purification was required, this could be achieved by extraction into 5–10% aqueous NaOH at room temperature, filtration through Celite, and precipitation with acetic acid or dilute HCl. A number of examples of isonitrosoacetanilides **2** prepared by this two-step procedure are shown in Table 1.

The two-step route to isonitrosoacetanilides is comparable to the standard Sandmeyer method[1,2] in a number of cases, although in the case of anilines with electron rich *ortho*-substituents (e.g., **1b**,**r**,**s**,**v**) it is clearly superior to both the Sandmeyer and alternative literature routes.[11] In addition, in the case of lipophilic and less water soluble amines such as 2-aminobiphenyl (**1f**) the product yield is significantly improved (90% vs 42%) over that obtained by the traditional procedure.[19]

In conclusion, we have developed a new route to isonitrosoacetanilides that provides access to a wide variety of isatin derivatives. The route offers two distinct advantages over literature methods in that it can be equally used with aniline derivatives containing electron rich *ortho*-substituents, and also with those having poor aqueous solubility.

Table 1. Synthesis of substituted isonitrosoacetanilides[15]



	R	Yield[a] (%)	Lit. yield[b] (%)
a	H	87	80–91[2]
b	2-OCH_3	82	60.3[c,11]
c	2-NO_2	55	47.8[20]
d	2-Cl	81	85–89[d,7]
e	2-I	85	76[21]
f	2-Ph	90	42[19]
g	2-OPh	80	—[e]
h	3-OMe	63	42[22]
i	3-Cl	65	40[22]
j	4-CH_3	91	96–99[d,7]
k	4-Br	80	90[23]
l	4-CO_2Et	85	85[23]
m	4-CN	87	—[e]
n	4-NO_2	82	88[f,24]
o	2,3-$(CH_3)_2$	83	64[24]
p	2,3-Cl_2	84	66[25]
q	2-NO_2-3-CH_3	73	—[e]
r	2-OCH_3-5-Cl	90	38.5[c,11]
s	2,4-$(OCH_3)_2$	60	—[g]
t	2,4-Cl_2	87	—[g]
u	2,5-Cl_2	87	68[24]
v	2,5-$(OCH_3)_2$	90	75.5[c,11]
w	2,5-$(CH_3)_2$	78	78[26]

[a] Combined isolated yields for two steps.
[b] Sandmeyer method[1,2] unless otherwise noted.
[c] Five-step nitrone method.
[d] Ethanol co-solvent.
[e] All new compounds gave satisfactory spectral and analytical data.[27]
[f] Microwave procedure.
[g] Lit. yield not given.[28]

References and notes

1. Sandmeyer, T. *Helv. Chim. Acta* **1919**, *2*, 234–242.
2. Marvel, C. S.; Hiers, G. S. *Org. Synth.* **1941**, *1*, 327–330.
3. Sumpter, W. C. *Chem. Rev.* **1944**, *34*, 393–434.
4. Bayer, O.; Eckert, W. *Methoden zur Herstellung und Umwandlung von Isatinen*. In *Houben-Weyl, Methoden der Org. Chemie*; Thieme: Stuttgart, 1968; Bd. VII/4, pp 1–31.
5. Popp, F. D. *Adv. Heterocycl. Chem.* **1975**, *18*, 1–58.
6. Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273–324.
7. Garden, S. J.; Torres, J. C.; Ferreira, A. A.; Silva, R. B.; Pinto, A. C. *Tetrahedron Lett.* **1997**, *38*, 1501–1504.
8. Jnaneshwara, G. K.; Bedekar, A. V.; Deshpande, V. H. *Synth. Commun.* **1999**, *29*, 3627–3633.
9. Kollmar, M.; Parlitz, R.; Oevers, S. R.; Helmchen, G. *Org. Synth.* **2003**, *79*, 196–203.

10. Krapcho, A. P.; Cadamuro, S. A. *Org. Prep. Proced. Int.* **2004**, *36*, 74–76.
11. Prinz, W.; Kayle, A.; Levy, P. R. *J. Chem. Res. (M)* **1978**, 1347–1370.
12. Taylor, A. *J. Chem. Res. (M)* **1980**, 4154–4171.
13. McCaully, R. J.; Conklin, G. L. U.S. Patent 3,663,605, 1972; *Chem. Abstr.* **1972**, *77*, 61616.
14. Synthesis of 2,2-diacetoxyacetyl chloride (**5**): A mixture of 51.8 g (0.35 mol) of 50% w/w aqueous glyoxylic acid, 350 mL of acetic anhydride and 80 mL of glacial acetic acid were heated under reflux for 2 h, and the solvents were removed on a rotary evaporator. After azeotropic removal of remaining volatiles with toluene, the residual oil was dissolved in a mixture of 175 mL of CH_2Cl_2 and 90 mL of $SOCl_2$, and heated under gentle reflux for 30 min. The volatiles were removed under vacuum, an additional 75 mL of CH_2Cl_2 was added, and the mixture was re-evaporated to remove remaining volatiles. The residue was then distilled under vacuum to give 45.5 g (67% yield) of **5**: bp 58–59 °C (0.5 mm Hg); ^{1}H NMR ($CDCl_3$): δ 6.92 (s, 1H, CH), 2.22 (s, 6H, CH_3); ^{13}C NMR: δ 168.0 (C), 167.4 (C), 87.9 (CH), 20.3 (CH_3).
15. General procedure for the synthesis of isonitrosoacetanilides: The aniline **1** (4 mmol) and potassium hydrogencarbonate (2.0 g, 20 mmol) in dichloromethane (10 mL) were cooled to −10 °C. A solution of freshly distilled 2,2-diacetoxyacetyl chloride[11] (1.0 g, 5.2 mmol) in dichloromethane (5 mL) was added dropwise. The mixture was removed from the cooling bath and allowed to warm to room temperature. When the complete consumption of the aniline **1** was confirmed by TLC, the solid was removed by filtration, washed well with dichloromethane, and the filtrate was concentrated. Hydroxylamine hydrochloride (1.4 g, 20 mmol) was dissolved in a mixture of ethanol (10 mL) and water (5 mL), and the solution was then added to the crude diacetates **4**. The mixture was heated under reflux for 2 h, cooled to room temperature, and concentrated on a rotary evaporator until precipitation commenced. Water was then added to precipitate further product. The solid isonitrosoacetanilide **2** was collected by filtration and washed with water. Purification was by recrystallization or reprecipitation from 5% aqueous NaOH solution with acetic acid.
16. Petrov, A. S.; Somin, I. N.; Kuznetsov, S. G. *Zh. Org. Khim.* **1965**, *1*, 1434–1437; *J. Org. Chem. USSR (Engl. Transl.)* **1965**, *1*, 1454–1457.
17. (a) Baganz, H.; Domaschke, L. *Chem. Ber.* **1959**, *92*, 3170–3174; (b) Baganz, H.; Domaschke, L.; Kruger, K. E. *Chem. Ber.* **1959**, *92*, 3167–3170.
18. Bach, K. K.; El-Seedi, H. R.; Jensen, H. M.; Nielsen, H. B.; Thomsen, I.; Torssell, K. B. G. *Tetrahedron* **1994**, *50*, 7543–7556.
19. Batt, D. G.; Jones, D. G.; La Greca, S. *J. Org. Chem.* **1991**, *56*, 6704–6708.
20. Buchman, E. R.; McCloskey, C. M.; Seneker, J. A. *J. Am. Chem. Soc.* **1947**, *69*, 380–384.
21. Lisowski, V.; Robba, M.; Rault, S. *J. Org. Chem.* **2000**, *65*, 4193–4194.
22. Sadler, P. W. *J. Org. Chem.* **1956**, *21*, 169–170.
23. Varma, R. S.; Khan, I. A. *Curr. Sci.* **1978**, *47*, 114–115.
24. Baker, B. R.; Schaub, R. E.; Joseph, J. P.; McEvoy, F. J.; Williams, J. H. *J. Org. Chem.* **1952**, *17*, 149–156.
25. Buscarons, F.; Sanchez Moreno, L. *Analitica* **1967**, *21*, 191–201.
26. Gronowitz, S.; Hansen, G. *Ark. Kemi.* **1967**, *27*, 145–151.
27. Compound **2g**: mp 92–94 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (br s, 1H, exchangeable with D_2O), 8.46 (dd, $J = 8.1$, 1.6 Hz, 1H), 8.02 (br s, 1H, exchangeable with D_2O), 7.56 (s, 1H), 7.38–7.33 (m, 2H), 7.17–7.10 (m, 2H), 7.05–7.01 (m, 3H), 6.86 (dd, $J = 8.1$, 1.4 Hz, 1H). Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.72; N, 10.93. Found: C, 65.88; H, 4.62; N, 10.90. Compound **2m**: mp 180–184 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.27 (br s, 1H, exchangeable with D_2O), 10.55 (br s, 1H, exchangeable with D_2O), 7.89 (d, $J = 8.9$ Hz, 2H), 7.79 (d, $J = 8.9$ Hz, 2H), 7.66 (s, 1H). Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.37; H, 3.83; N, 22.44. Compound **2q**: mp 139–141 °C; ^{1}H NMR ($CDCl_3$): δ 9.61 (br s, 1H, exchangeable with D_2O), 8.38 (br s, 1H, exchangeable with D_2O), 8.23 (d, $J = 8.3$ Hz, 1H), 7.58 (s, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 7.7$ Hz, 1H), 2.44 (s, 3H). Anal. Calcd for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.83. Found: C, 48.69; H, 4.15; N, 18.88.
28. Baruffini, A.; Borgna, P.; Pagani, G.; Ponci, R. *Farmaco, Ed. Sci.* **1967**, *22*, 590–611.