## Synthetic Applications of <u>N</u>-Aryl-<u>O</u>-acyl Hydroxamic Acids. A Convenient Route to 3-Substituted <u>N</u>-Benzoyl Oxindoles

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Abstract.— The enol silulethers of N-acyloxybenzanilides undergo smooth rearrangement to afford o-aminobenzoyl-phenylacetic acids and thence to oxindoles by dehydration.

Oxindoles (1), appropriately substituted at both nitrogen and C-3, occupy a pivotal position in the synthesis of biologically active alkaloids<sup>1</sup> incorporating a pyrrolo[2,3-b] indole moiety. Our interest in the synthesis of these and other related molecules<sup>2</sup> prompted us to study the chemistry of N-aryl-O-substituted acetylhydroxamic acids as potential precursors for the title compounds.



Reagents and conditions: i)  $R_1R_2CHC(O)Cl$ , py or  $R_1R_2CHCO_2H$ , DCC, DMPA; ii) LDA, THF, -90 °C; iii) TMSCl; iv) -90 to +15 °C,  $H_2O$ ; v) DCC,  $CH_2Cl_2$ , r.t.; vi)  $\Delta$ 

Scheme

Entry	R	2 R1 I	32	Yield,% <sup>a</sup>	mp°C solvent	5,Yield,% <sup>a</sup>	mp°C solvent	
1	Н	н	н	92	57.5 Et <sub>2</sub> O	8 <sup>b</sup>	184-185 <sup>0</sup> Et <sub>2</sub> O-hexane	
2	Н	н	Ph	72	68-70 Et <sub>2</sub> O-hexan	e <sup>68</sup> d	174-175 EtOH - H <sub>2</sub> O	
3	Н	Ph	Ph	73	125 EtOAc	25 <sup>d,e</sup>	165-167 Et2O	
4	Н	Н	SPh	76	62 Et <sub>2</sub> O	50 <sup>d</sup>	oil	
5	CI	Н	SPh	69	95 Et <sub>2</sub> O	50d	119-120 Et <sub>2</sub> O	
6	CO <sub>2</sub> Me	Н	SPh	89	96-97 Et <sub>2</sub> O	54d	93-95 hexane	
7	Me	Н	SPh	72	74-75 Et <sub>2</sub> O	71 <sup>d</sup>	94-95 hexane	
8	6			55	105 Et <sub>2</sub> O	20 <sup>e,f</sup>	157-159 hexane	
9	7			68	124-125 EtOAc	g	g	

Table	1.— Synthesis	of N-Aryl-O-acyl	Hydroxamic	Acids	(2)	and	Products	of
	Rearrange	ment (5)						

<sup>a</sup> Represent yields of products purified by column chromatography and/or crystallisation. <sup>b</sup> Recovered parent hydroxamic acid (90%). <sup>c</sup> Lit.<sup>10</sup> mp 179 ° C . <sup>d</sup> Characterised as methyl esters. <sup>e</sup> The corresponding benzanilide was isolated in *ca.* 40% yield. <sup>f</sup> Product of rearrangement **8** characterised as methyl ester. <sup>g</sup> See Table 2, entry 8.

N-acyloxybenzanilides 2 (Scheme) are readily obtained from the corresponding hydroxamic acids in good yields by esterification with acid chlorides (pyridine-CH<sub>2</sub>Cl<sub>2</sub>) or with substituted acetic acids<sup>3</sup> (DCC-DMAP). Esters of this type have been shown to rearrange<sup>4</sup> thermally to the corresponding o-acyloxybenzanilides (3). However, silylethers 4, generated *in situ* from them with LDA (3 eq) in THF at -90° C and subsequent reaction with TMSCl (5 eq) at the same temperature, when allowed to warm to room temperature and quenched with water afforded the o-aminobenzoyl-phenylacetic acids<sup>5</sup> 5.

Entry	1	1		Yield, % <sup>a</sup>	mp°C
	R	R1	R <sub>2</sub>		solvent
1	Н	н	Ph	65	175-176 <sup>b</sup> EtOH
2	н	Ph	Ph	25 <sup>c</sup>	164-165 Et <sub>2</sub> O
3	н	н	SPh	46	104-105 Et <sub>2</sub> O
4	CI	н	SPh	49	121-122 Et <sub>2</sub> O-hexane
5	CO <sub>2</sub> Me	н	SPh	51	151-152 CHoClo-bexane
6	Ме	н	SPh	53	143-145 Et <sub>2</sub> O-hexane
7	OMe	н	SPh	34	101-102 CH <sub>2</sub> Cl <sub>2-hexane</sub>
8	10			20 <sup>c</sup> .ď	83-84 Hexane

Table 2.— 3-Substituted N-Benzoyl Oxindoles (1)

<sup>a</sup> Represent overall yields from 2 of products purified by column chromatography and/or crystallisation. <sup>b</sup> Lit.11m p 175.5° C. <sup>c</sup> The corresponding benzanilide was isolated in *ca.* 40% yield. <sup>d</sup> This oxindole was obtained directly from 7.



The results (**Table 1**) show that the presence of carbanion stabilising groups (SPh, Ph or olefin)  $\alpha$  to the carbonyl function in the acetyl fragment of 2 is necessary to prevent a rapid reversion to the parent hydroxamic acid (entry 1) and to favour the rearrangement.<sup>6</sup> Functional groups such as OMe,<sup>7</sup> Cl and CO<sub>2</sub>Me do not seriously interfere with the reaction. These acids (5) were quantitatively cyclised to the corresponding oxindoles<sup>8</sup> 1 by dehydration with DCC (r.t.; CH<sub>2</sub>Cl<sub>2</sub>). Alternatively, it was found more advantageous, from the practical standpoint, to treat the crude reaction mixture, obtained after aqueous work-up, directly with DCC and isolate the oxindoles formed (**Table 2**) by column chromatography. Of particular synthetic interest is the ready access the method provides for phenylthio-oxindoles (entries 4-7), with the nitrogen already suitably protected, thus permitting further useful chemical transformations to be performed at C-3 by radical and/or carbanion chemistry.

In summary, a general and an expeditious route for the construction of N-protected oxindoles,<sup>9</sup> involving a formal 3,3-sigmatropic rearrangement of hydroxamic acid derived ketene silylketal intermediates under exceptionally mild conditions is reported.

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## **REFERENCES AND NOTES**

- Yu, Q-S; Brossi, A. Heterocycles, 1988, 27, 7/; Shishido, K.; Shitara, E.; Komatsu, H.; Hiroya, K.; Fukumoto, K.; Kametani, T. J. Org. Chem., 1986, 51, 3007/; Cozzi, P. G.; Palazzi, C.; Potenza, D.; Scolostico, C.; Sun, W. Y. Tetrahedron Lett., 1990, 25, 5661.
- 2. Hendrickson, J. M.; R. Rees, R.; Goschke, R. Proc. Chem. Soc., 1962, 383.
- 3. Hassner, A.; Alexanian, V. Tetrahedron Lett., 1978, 46, 4475 .
- See Horner, L.; Steppan, H. Justus Liebigs Ann. Chem., 1957, 606, 24 and Ohta, T.; Shudo, K.; Okamoto, T. Tetrahedron Lett., 1978, 23, 1983, for thermal rearrangement of this type of esters to the corresponding o -acyloxybenzanilides.
- 5. Other products formed in the reaction are the benzanilides, hydroxamic acids (traces) and p-substituted phenylacetic acids  $(10 \sim 17\%)$  when R=H in 2 (Table 1, entries 2,3,4 and 9).
- 6. For a recent review on the synthetic use of hydroxylamines and their derivatives involving hetero-Cope rearrangements see: Blechert, S. *Synthesis*, **1989**, 71.
- 7. The ester **9** which thermally rearranges to the corresponding *o*-acetoxybenzanilides with extreme ease was prepared as follows: The hydroxamic acid in THF was reacted with ter-BuLi (1 eq) at -100° C, followed by addition of the acid chloride (1.2 eq). After the reaction was complete (t.l.c. control), the silyl ether was generated by an additional equivalent of ter-BuLi and TMSCl (3 eq). The reaction was brought to completion by allowing the mixture to attain room temperature and the product isolated as the oxindole.
- For the preparation and chemistry of oxindoles see: Brown, R. T.; Joule, J. A.; Sammes, P. G. in Comprehensive Organic Chemistry; Barton, D. H. R.; W. D. Ollis, W. D. Eds.; Pergamon Press: Oxford, 1979; vol. IV, p. 446.
- 9. All new compounds were adequately characterised by elemental analysis or accurate mass measurements. Their spectral data (IR, <sup>1</sup>H NMR) are in complete accordance with the assigned structures.
- 10. Neber, P. W. Ber., 1922, 55, 826.
- 11. Bruce, J. M.; Sutcliffe, F. K. J. Chem. Soc., 1957, 4789.

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