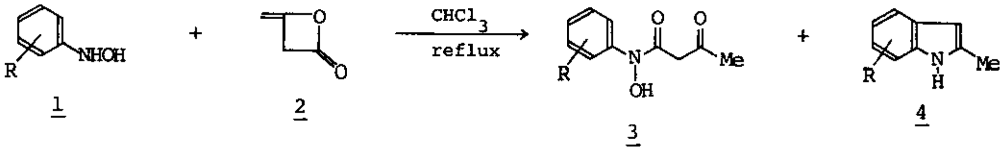
MELDRUM'S ACID IN ORGANIC SYNTHESIS 3. SYNTHESIS OF 2-SUBSTITUTED INDOLES FROM PHENYLHYDROXYLAMINE

Kunihiko Mohri, Yuji Oikawa,* Ken-ichi Hirao, and Osamu Yonemitsu
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

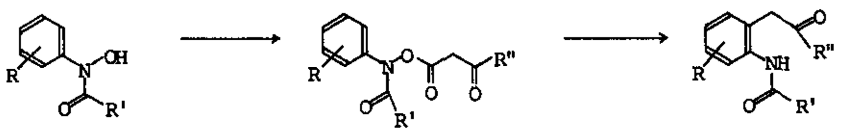
Abstract —— Treatment of phenylhydroxylamine oxalate with acyl Meldrum's acids in boiling acetonitrile readily gave N-acylacetylphenylhydroxylamines, which were converted to 2-substituted indoles by another treatment with acyl Meldrum's acids in refluxing toluene. N-Benzoyl, N-acetyl, and N-benzyloxycarbonyl derivatives of phenylhydroxylamine were treated with phenylacetyl Meldrum's acid in boiling benzene, followed by treatment with hydrochloric acid in ethanol to give the corresponding N-acyl-2-benzylindoles.

There are a number of methods for synthesis of the indole ring which is found in so many biologically important compounds,[1] a convenient and widely useful synthetic method of 2-substituted indoles, however, is still desired to establish.[2] We have reported some synthetic applications of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione),[3] a convenient one-pot synthesis of indole propionates[4] and a general and versatile synthesis of β-keto esters.[5] This communication describes a preliminary work for a useful synthesis of 2-substituted indoles as an extended synthetic application of Meldrum's acid.

Five years ago, Kato et al. reported the reaction of phenylhydroxylamines and diketene in the course of their extensive studies of ketene:[6] Phenylhydroxylamines (1) reacted with diketene (2) at 0°C to give their N-acetoacetyl derivatives (3) in good yields as reported previously by Matter et al.,[7] but when a chloroform solution of 1 and 2 was refluxed, a complex mixture containing 3



R=H,Me,Cl,Br



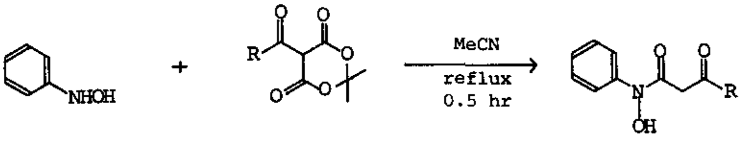
5 6 7

R=H,Me,Cl,CO_2Me; R'=Me,C_6H_5; R"=Me,C_6H_5

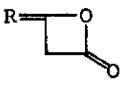
(37-65%) and a 2-methylindole (4, 5-21%) was obtained. Coates *et al.* subsequently reported an improved synthesis of 2-methyl- and 2-phenylindoles:[8] An N-acetyl- or N-benzoylphenylhydroxylamine (5) was condensed with 2 or benzoylacetic acid to give 6, which was converted to a rearranged *ortho* alkylation product (7) by heating in toluene in 28-66% overall yield from 5. This method for the synthesis of 2-substituted indoles looks promising, but is usually limited to the synthesis of 2-methyl and 2-phenyl derivatives, because other arbitrary β-keto acids and their equivalents are not so easily available.

An acyl Meldrum's acid (9),[5] easily available from Meldrum's acid[3] and carboxylic acid or its chloride, has a high reactivity toward nucleophiles, and is a synthetic equivalent for a β-keto acid having an activated carboxylic group, in other words, for a mixed diketene (11). Because 9 is an efficient and convenient acylacetylation agent, an arbitrary N-acylacetylphenylhydroxylamine (10) is expected to obtain by the reaction of 9 and phenylhydroxylamine (8).

When an equimolar acetonitrile solution of acetyl Meldrum's acid (9a) and 8-oxalate was refluxed for 30 min, N-acetoacetylphenylhydroxylamine (10a) was obtained quite easily in a high yield. This simple method was applied to a variety of acyl Meldrum's acids (9b-i) to prepare various 10b-i having alkyl, phenyl, benzyl, ester, and ether substituents (Table I). Every 10 has an anilide absorption band at 1670-1685 cm^{-1} in its ir spectrum, which clearly indicates that 10 is not an O-acylacetyl compound.[9]



8 9 10

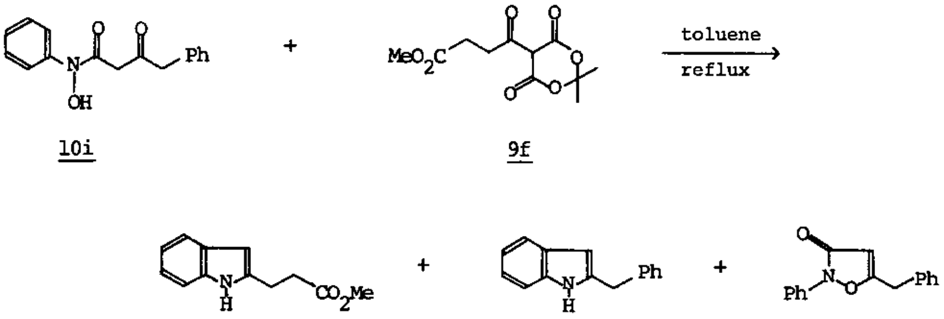


11

Table I. Preparation of N-Acylacetylphenylhydroxylamines (10) from Phenylhydroxylamine (8) and Acyl Meldrum's Acids (9).

10	R	yield,%	mp°C(solvent)	ir(Nujol),cm^{-1}
a	CH_3	84	124-126(benzene-hexane)	3275,1670,1595
b	CH_3CH_2	95	135-136(benzene)	3275,1670,1595
c	$(CH_3)_2CH$	60	94-95(benzene)	3250,1670,1595
d	$CH_3CH_2O(CH_2)_2$	76	87-88(benzene)	3225,1670,1590
e	$CH_3CO_2(CH_2)_2$	74	115-116(EtOAc)	3250,1735,1675,1595
f	$CH_3O_2C(CH_2)_2$	91	87-88(benzene)	3225,1725,1670,1595
g	$CH_3O_2C(CH_2)_3$	51	92-94(ether)	3240,1725,1675,1595
h	C_6H_5	93	136-137(benzene)	3050,1685,1630,1590
i	$C_6H_5CH_2$	90	132-134(benzene)	3250,1670,1590

Since it was expected that treatment of 10 with 9 would give an ortho Alkylation product via a Carroll type rearrangement[10] of an O-acylacetyl derivative of 10, a toluene solution of 10i and 9f was heated under reflux for 2 hr. Two indoles, 12f and 12i, and an isoxazolone (13i) were isolated in 22, 5, and 28% yields, respectively. No expected ortho alkylation product corresponding to 7 was isolated, and further reactions took place to afford the final indoles (12f,i). The main indole (12f), though in a poor yield, was probably formed through a series of O-acylacetylation, a Carroll type rearrangement, decarboxylation, dehydrative cyclization, and deacylation as shown in the following scheme. The side reaction product (13i) and the minor indole (12i) were probably formed by a catalytic dehydration of 10i with acidic 9f[11] and by a thermal reaction of 10i itself,[12] respectively.



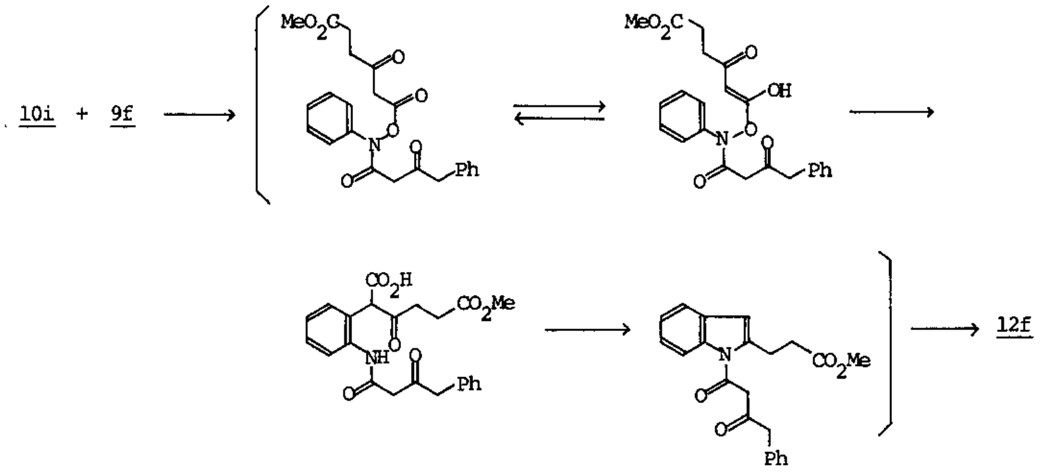
10i

9f

12f

12i

13i



When 10 was heated with the corresponding acyl Meldrum's acid (9) (both 10 and 9 have the same R group), the expected indole (12) was isolated after chromatographic purification, though sometimes accompanied by 13 (Table II).

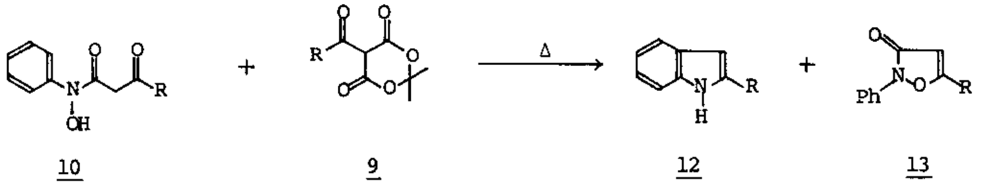


Table II. Thermal Reaction of 10 and the Corresponding 9

	12 yield,%	mp°C(solvent)	ir(Nujol),cm^{-1}	13 yield,%
b	21	45-46.5(pet. ether)[13]		46
e	40	76-77(hexane)	3300,1700	-
f	58	97-98(hexane)	3350,1715	3
g	38	64-66(hexane)	3350,1720	-
i	50	85-86(hexane)[13]		20

If an N-acylphenylhydroxylamines (14-16) instead of 8 itself is used as a starting material in analogy with the procedure by Coates et al.,[8] 9 in amounts equimolar with 14-16 must be sufficient for the indole formation. Equimolar amounts of 14 and 9i were refluxed in toluene to give mainly

9i

14: R=COPh
15: R=COMe
16: R=CO_2CH_2Ph

17
18
19

20
21
22

an *ortho* alkylation product (17), which was converted to N-benzoyl-2-benzylindole (20) by further heating in xylene.

In order to find milder conditions, when a benzene solution of 14 and 9i in the presence of Cu powder was refluxed for 1 hr under argon, 17 was easily isolated in 64-67% yield. Similarly, 15 and 16 gave 18 and 19, respectively (Table III). Treatment of 17 with 10% hydrochloric acid-ethanol (0.6:1) under reflux for 20 min gave 20 in 79% yield. Practically, 20 was obtained from 14 and 9i without isolation of the intermediary 17: After removal of the Cu powder and the solvent from the reaction mixture of 14 and 9i, the residue was dissolved in the hydrochloric acid-ethanol, and the solution was refluxed for 20 min to give 20 (Table III). The benzoyl group of 20 was easily removed by the treatment with sodium carbonate in aqueous methanol at room temperature to give 2-benzylindole quantitatively.

Table III. *ortho*-Alkylation Products (17-19) and N-Acyl-2-benzylindoles (20-22) from N-Acylphenylhydroxylamines (14-16) and Phenylacetyl Meldrum's Acid (9i)

product	yield,%	mp°C(solvent)	ir(Nujol),cm^{-1}
17	67	116-118(benzene-hexane)	3300,1705,1645,1600,1580
18	54	109-110(benzene)	3270,1705,1650,1580
19	56	100-102(benzene)	3260,1705,1690,1585
20	52[a]	88-89(ether)	3300,1685,1595
21	46[a]	oil	3375,1705,1615,1600
22	47[a]	68-70(ether-hexane)	3300,1735,1600

[a] Overall yields from 14-16.

Some improvements of this new 2-substituted indole synthesis, their synthetic applications, and detailed mechanistic studies will be reported soon.[14]

References and Notes

1. R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970; R. K. Brown, "Indoles", W. J. Houlihan, Jr., Ed., Wiley-Intersciences, New York, 1972; J. E. Nordlander, D. Catalane, K. D. Katian, R. M. Stevens, and J. E. Haky, *J. Org. Chem.*, **46**, 778 (1981), and references cited therein.
2. Recently, a promising synthesis of 2-substituted indoles has been reported: M. L. Corre, A. Hercouet, and H. L. Boron, *J. C. S. Chem. Comm.*, **1981**, 14
3. A. N. Meldrum, *J. Chem. Soc.*, **93**, 598 (1908); D. Davidson and S. A. Bernhardt, *J. Am. Chem. Soc.*, **70**, 3426 (1948).
4. Y. Oikawa, H. Hirasawa, and O. Yonemitsu, *Tetrahedron Lett.*, **1978**, 1759.
5. Y. Oikawa, K. Sugano, and O. Yonemitsu, *J. Org. Chem.*, **43**, 2087 (1978).
6. T. Kato, K. Tabai, and E. Kawashima, *Chem. Pharm. Bull.*, **24**, 1544 (1976).
7. M. Matter, C. Vogel, and R. Rosshard, Ger. Patent, 1146494 [*Chem. Abstr*, **59**, 10058g (1963)].
8. R. M. Coates and I. M. Said, *J. Am. Chem. Soc.*, **99**, 2355 (1977).
9. *Cf*. A. R. Katritzky, S. Øksne, and A. J. Boulton, *Tetrahedron*, **18**, 777 (1962); M. Fujimoto and M. Sakai, *Chem. Pharm. Bull.*, **13**, 248 (1965).
10. M. F. Carroll, *J. Chem. Soc.*, **1940**, 704, 1266; **1941**, 507; W. Hoffmann, H. Paseduch, H. Pommer, and W. Reif, *Liebigs Ann. Chem.*, **747**, 60 (1971).
11. The acid-catalyzed formation of various 5-substituted isoxazolin-3-ones (13) will be reported in the succeeding communication.
12. The direct thermal formation of 12 from 10 may provide a convenient and useful synthetic method for 2-substituted indoles, and will be reported with its mechanistic studies soon.
13. M. H. Palmer and P. S. McIntyre, *J. Chem. Soc.* (*B*), **1969**, 446.
14. All new products have satisfactory spectral and elementally analytical data.

Received, 10th December, 1981