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New Route to 2-Substituted Indoles by Pyrolysis of N-Acylacetylphenylhydroxylamines

Ken-ichi HIRAO,[†*] Kunihiko MOHRI,[††1] Osamu YONEMITSU[††*]
Masayoshi TABATA,[†††] and Junkichi SOHMA,[†††]

[†] Department of Chemistry, Faculty of Science,
Hokkaido University, Sapporo 060, Japan
[††] Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan
[†††] Faculty of Engineering, Hokkaido University, Sapporo 060, Japan

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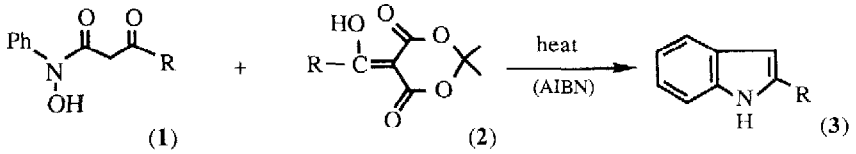
Abstract: Convenient and regiospecific synthesis of 2-substituted indol (**3**) by thermolysis of *N*-acylacetylphenylhydroxylamine (**1**) and its mechanism including the formation of a radical intermediate are reported.

The development of methods for synthesis and selective functionalization of the indole nucleus has been noted as an important subject because of its wide spread distribution in pharmaceutically active compounds.[2,3] Beginning with the well-known Fischer indole synthesis,[2,4] there have been many reports on various synthetic methods of indoles.[3] However, convenient and regiospecific methods for the preparation of 2-substituted indoles are still requested. We previously reported[5] a versatile method for



(**1**) (**2**) (**3**)

a R : - CH_3
b R : - CH_2CH_3
c R : - $CH(CH_3)_2$
d R : - $CH_2CH_2OCH_2CH_3$
e R : - $CH_2CH_2COOCH_3$
f R : - C_6H_5
g R : - $CH_2C_6H_5$

the synthesis of 2-substituted indoles (**3**) by the thermal reaction of *N-acyl*acetylphenylhydroxylamines (**1**)[6] and *acyl* Meldrum's acids (**2**)[7] having the *same acyl* group. The multistep reaction mechanism was also discussed. In these studies it was found that when **2e** was reacted with **1g** having a *different acyl* group from each other, along with **3e** (22%), 2-benzylindole (**3g**), derived directly from **1g**, was obtained though in a low yield (5%).

Thus, in fact, **3g** was obtained in a 67% yield when **1g** was simply heated in xylene (Table 1). The direct conversion of other hydroxylamines (**1**) to the various 2-substituted indoles (**3**) was realized concurrently (Table 2).[8] Although the yields of products in these reactions are moderate (43-67%),[9] the ready availability of a variety of **1** and the simple reaction procedures mean that the reaction will provide a useful method for the selective preparation of 2-substituted indoles.

The reaction sequence seems to consist of multisteps. In order to learn the unequivocal mechanistic features, we examined the reaction in more detail using **1g** as a representative example. When a xylene solution of **1g** was heated under reflux in the

Table 1. Direct formation of 2-benzylindole (**3g**) from *N*-acetoacetylhydroxylamine (**1g**)

Entry	Solvent	Conditions	Yield/%
1	Benzene	Reflux, 16 h	0
2	Benzene	140°C, 2 h	53
3	Toluene	Reflux, 15 h	58
4	Xylene	Reflux, 2 h	67

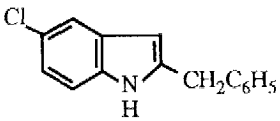
Table 2. Thermal reaction of **1**[*]

1	Yield of 3/%
a	43
b	46
c	45
d	53
e	52
f	55
g	67 (82)[**]

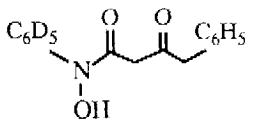
[*]Refluxed in xylene for 1-2 h.

[**]In the presence of AIBN. See the text.

presence of azobisisobutyronitrile (AIBN), a radical initiator, the reaction was completed in 35 min giving **3g** in a 82% yield. On the contrary, diphenylpicrylhydrazyl (DPPH), a radical trapping agent, completely inhibited the reaction. This behavior provides evidence for the fact that the reaction should occur through a radical intermediate. In addition, the xylene solution of equimolar quantities of **1g** and *p*-chloronitrosobenzene under reflux gave 2-benzyl-5-chloroindole (**4**, 18%) together with **3g** (21%).

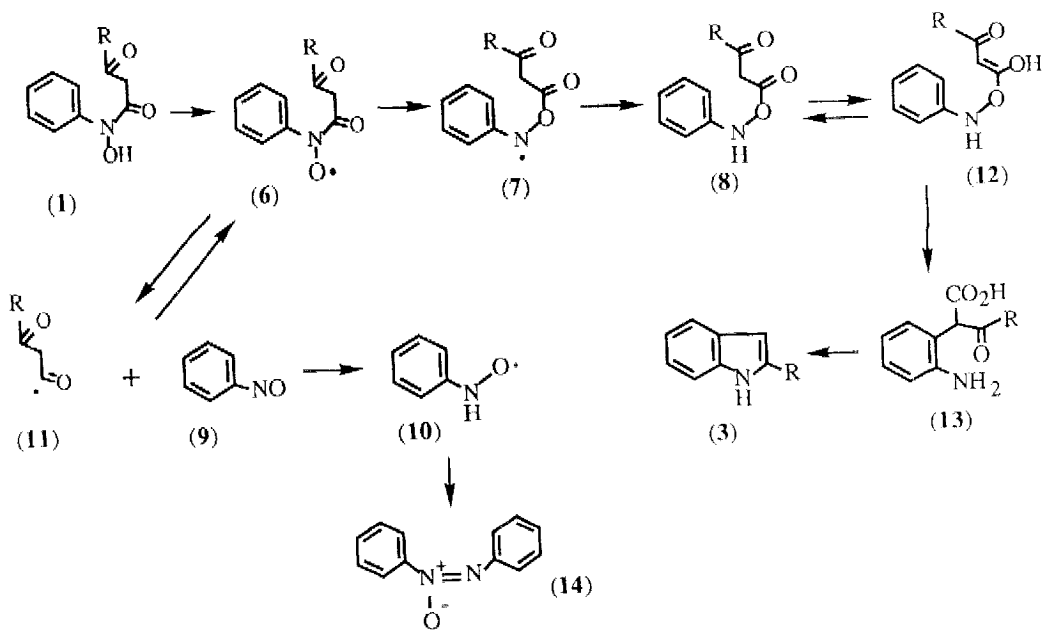


(**4**)



(**5**)

To obtain a further insight into the reaction, ESR spectra of the xylene solution of **1g** (0.1M) were taken under argon atmosphere at temperatures of 80 to 170°C. At 80°C (Cf. Table 1, Entry 1) a signal being responsible for the phenyl nitroxide (**10**)[10] was gradually generated. At temperatures near 140°C (Cf. Table 1, Entry 4) the spectrum became complicated, showing the formation of a new radical species. By using hydroxylamine-d_5 (5), a simplified spectrum was obtained. The species can be distinguished from **10** and readily recognized to have an anilino radical structure (**7**)[11] on the basis of the splitting pattern of the signals (a^N = 10.5G, g = 2.0051, triplet).



By considering these results, a pathway to the 2-substituted indole (**3**) may be introduced. Acylnitroxide (**6**), initially formed by the homolytic cleavage of the O-H bond of **1** rearranges above 140°C into the anilino radical (**7**),[12] which then recombines with a hydrogen radical to give *O*-acylacetylphenylhydroxylamine (**8**). The subsequent [3,3] sigmatropic rearrangement, decarboxylation and dehydrocyclization, then provides **3**. The formation of nitrosobenzene (**9**) from **6** also takes place and these are in equilibrium with each other. At lower temperature (80°C) acylnitroxide (**6**) could not rearrange to the anilino radical (**7**) and thus slowly decomposes to azoxybenzene (**14**) via **9**.

We are currrently pursuing further clarification of this mechanism.

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