HETEROCYCLES, Vol. 63, No. 6, 2004, pp. 1267 - 1271
Received, 9th February, 2004, Accepted, 5th April, 2004, Published online, 9th April, 2004

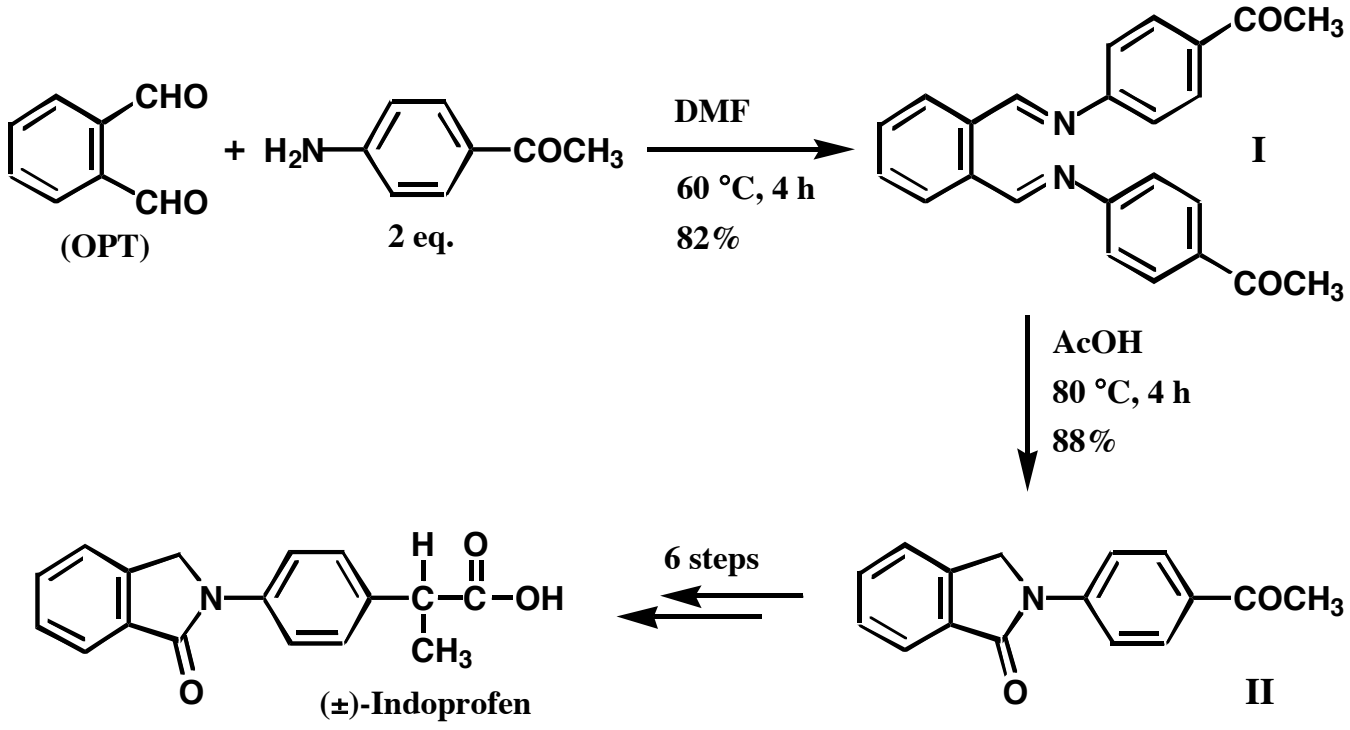
STUDIES OF ISOINDOLES. 12.[1] A STRUCTURAL REVISION OF THE 1:2 MANNICH TYPE CONDENSATION REACTION PRODUCT FORMED FROM *o*-PHTHALALDEHYDE AND SUBSTITUTED ANILINE†

Ichiro Takahashi,*,[a] Rika Miyamoto,[a] Kenji Nishiuchi,[a] Minoru Hatanaka,[a] Akihito Yamano,[b] Akiyo Sakushima,[c] and Shinzo Hosoi*,[c]

[a]Department of Applied Chemistry and Biotechnology, Faculty of Engineering, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8507, Japan
[b]X-Ray Research Laboratory, Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8666, Japan
[c]Department of Pharmacognosy, School of Pharmaceutical Sciences, Kyushu University of Health and Welfare, 1714-1 Yoshino-cho, Nobeoka 882-8508, Japan

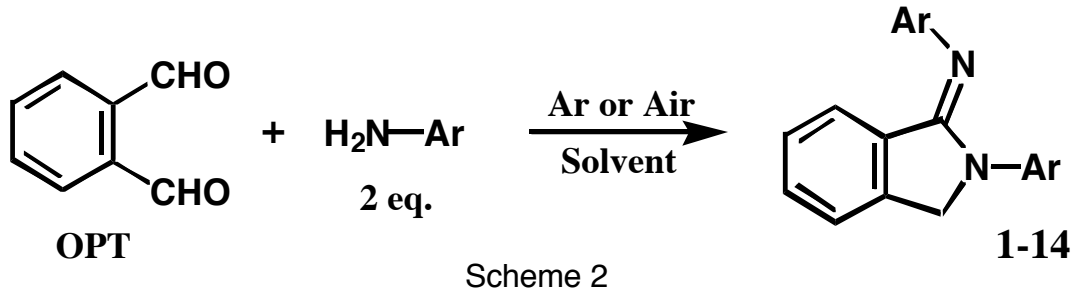
Abstract – The structure of the double Mannich condensation product from *o*-phthalaldehyde and substituted aniline was proved to be iminoisoindoline, but not diimine, based on *X*-Ray analysis.

Heterocyclic compounds containing phthalimidine (2,3-dihydroisoindol-1-one) skeletons have attracted considerable synthetic interest in recent years, as a number of fascinating natural/artificial bioactive compounds such as staurosporine (protein kinase C inhibitor), indoprofen (antiinflammatory agent) , and DN-2327 (also known as pazinaclone; anxiolytic agent) have been found to be clinically effective.[2,3] As reported previously, mild-condition phthalimidine synthesis based on a Mannich-type condensation reaction has usually required the use of some synthetic auxiliary in the reaction system.[4,5] Although phthalimidine synthesis, as reported by Kametani and co-workers, has only been utilized in the preparation of an indoprofen intermediate, the method has appeared to be useful because no additional auxiliary is needed.[6] As shown in Scheme 1, the method consists of two steps, namely the formation of "diimine" followed by cyclization, the latter of which has been assumed to involve acetic acid and *p*-aminoacetophenone (delivered from "diimine") as synthetic auxiliaries.[2] However, upon reexamination in our laboratory the reaction has turned out to be nonreproducible, which might be due to the questionable structure of the "diimine" intermediate. We wish to report herein on the general procedure for preparation of the so-called "diimine" intermediate in the Kametani phthalimidine synthesis, together with its structural revision to "iminoisoindoline" based on ^{1}H NMR spectra and *X*-Ray analysis.



Scheme 1

The general experimental procedure is as follows: *o*-Phthalaldehyde (OPT) and an aniline derivative (molar ratio = 1:2) were dissolved in ether, and the solution was stirred for 3-24 h to precipitate crude "diimine", which was then washed with ice-cold ether to give a pure sample. A small quantity of DMF was added when the poor solubility of intermediate components began to inhibit the reaction. The results are summarized in Table 1.



Scheme 2

In all the entries examined, products possessing a common framework (from ^{1}H NMR spectra) were found to be formed in fair to good isolated yields, indicating the generality of this method. The ^{1}H NMR spectral data of Kametani's "diimine" (**8**) are shown in Table 2, together with that of the corresponding phthalimidine derivative (**15 ≡ II**). The aromatic signals, which have been observed as a broad multiplet of 12H by Kametani and co-workers,[6] should be assignable as two sets of AA'XX' type signals (8H in total), together with two doublets (1H each, 2H in total) and two doubled-doublets (1H each, 2H in total). These findings indicate the presence of an unsymmetrically 1,2-substituted benzene structure and the lack of symmetry expected from a so-called "diimine" structure.

Table 1. Preperation of Iminoisoindolines.[a]

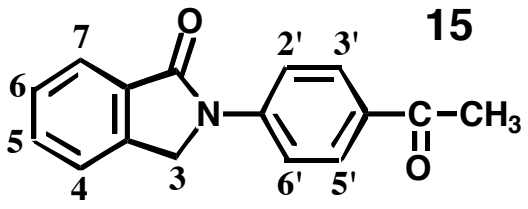
Run and Product No.	Ar-NH_2	Solvent /ml	Atmos-phere	Temp /°C	Time /h	Yield /%
1	*p*-NEt_2-C_6H_4-NH_2	Et_2O(25)	Ar	rt	4	21
2	*p*-OMe-C_6H_4-NH_2	Et_2O(25)	open[c]	rt	4	76
3	*p*-Me-C_6H_4-NH_2	Et_2O(25)	Ar	rt	24	34
4	C_6H_5-NH_2	Et_2O(25)	Ar	rt	24	66
5	*p*-Cl-C_6H_4-NH_2	Et_2O(19)	open[c]	rt	24	59
6	*p*-Br-C_6H_4-NH_2	Et_2O(25)	open[c]	rt	24	70
7	*p*-F-C_6H_4-NH_2	Et_2O(25)	Ar	rt	4	37
8[b]	*p*-COMe-C_6H_4-NH_2	DMF(30)	Ar	70	3	66
9	*p*-CO_2Me-C_6H_4-NH_2	Et_2O(25)+DMF(1)	Ar	rt	24	62
10	*p*-NO_2-C_6H_4-NH_2	Et_2O(20)+DMF(2)	open[c]	rt	24	96
11	*m*-OMe-C_6H_4-NH_2	Et_2O(25)	Ar	rt	24	51
12	*m*-Cl-C_6H_4-NH_2	Et_2O(25)	Ar	rt	24	68
13	1-$C_{10}H_7$-NH_2	Et_2O(20)+DMF(3)	open[c]	rt	24	52
14	2-$C_{10}H_7$-NH_2	Et_2O(25)	Ar	rt	24	84

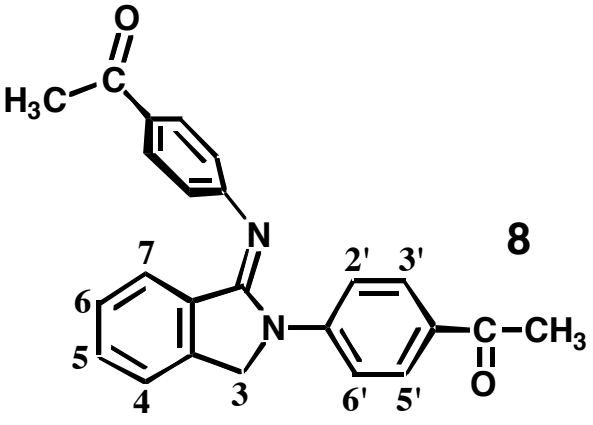
(a) Scale: OPT = 5 mmol, aniline = 10 mmol. (b) Re-run of the reaction in ref. 6. (c) Dried tube over $CaCl_2$ was used.

Table 2. Comparison of Chemical Shifts of ^{1}H NMR Spectra between Phthalimidine (15) and Iminoisoindoline (8)

Protons[a]	Compounds	
	15	**8**[b]
C3-2H	4.91	5.02 (+0.11)
C4-H	7.54	7.50 (-0.04)
C5-H	7.64	7.46 (-0.18)
C6-H	7.53	7.11 (-0.42)
C7-H	7.94	6.78 (-1.16)
C2',6'-2H	8.03	8.02 (-0.01)
C3',5'-2H		8.11 (+0.08)
CH_3CO	2.61	2.59 or 2.64 (~0)

(a) Recorded at 400 MHz in $CDCl_3$ withTMS as an internal reference. (b) Chemical shift differences [δ_{ppm} (**8**) - δ_{ppm} (**15**)] are shown in parentheses. Negative values indicate upfield shifts.





In addition, to the best of our knowledge concerning diimines derived from terephthalaldehyde and primary amines,[7] proton signals assignable to C<u>H</u>=N groups should appear at δ ~ 8.5 ppm; the 2H singlet located at δ ~ 5.0 ppm should better be assigned as a benzylic CH_2 group (C3-2H). Taking into account the molecular weight of the compound being the same as that of "diimine", the revised structure was thus concluded to be "1-arylimino-2-arylisoindoline". Unfortunately, similar to the Diels-Alder cycloadduct reported previously,[1] it was difficult to apply 2D techniques in NMR for correlations across consecutive tertiary carbon units and N-C=N linkages. The stereostructure was directly determined to be (*E*)-form directly by *X*-Ray diffraction for 1-phenylimino-2-phenylisoindoline (**4**) (Figure 1).[8] In the crystal structure, hydrogens on the isoindoline phenyl ring apparently lay in a diamagnetic region induced by the phenyl ring attached to 1-imino nitrogen, and the extent of the diamagnetic effects increased according to the order of H(3), H(4), H(5), and H(6) as expected.[9] This finding was consistent with the trend in the term "chemical shift difference" [CSD; δ_{ppm} (iminoisoindoline) - δ_{ppm} (phthalimidine)], for which compounds (**8**) and (**15**) are shown in Table 2 as an example. In addition, similar CSD value tendencies were observed concerning all other iminoisoindolines as seen in Table 1. Overall results can be interpreted unambiguously, only if all iminoisoindolines prepared in the present study existed as (*E*)-forms in solution as well as in crystal. Further investigation of the convenient conversion of iminoisoindoline to phthalimidine is currently underway.

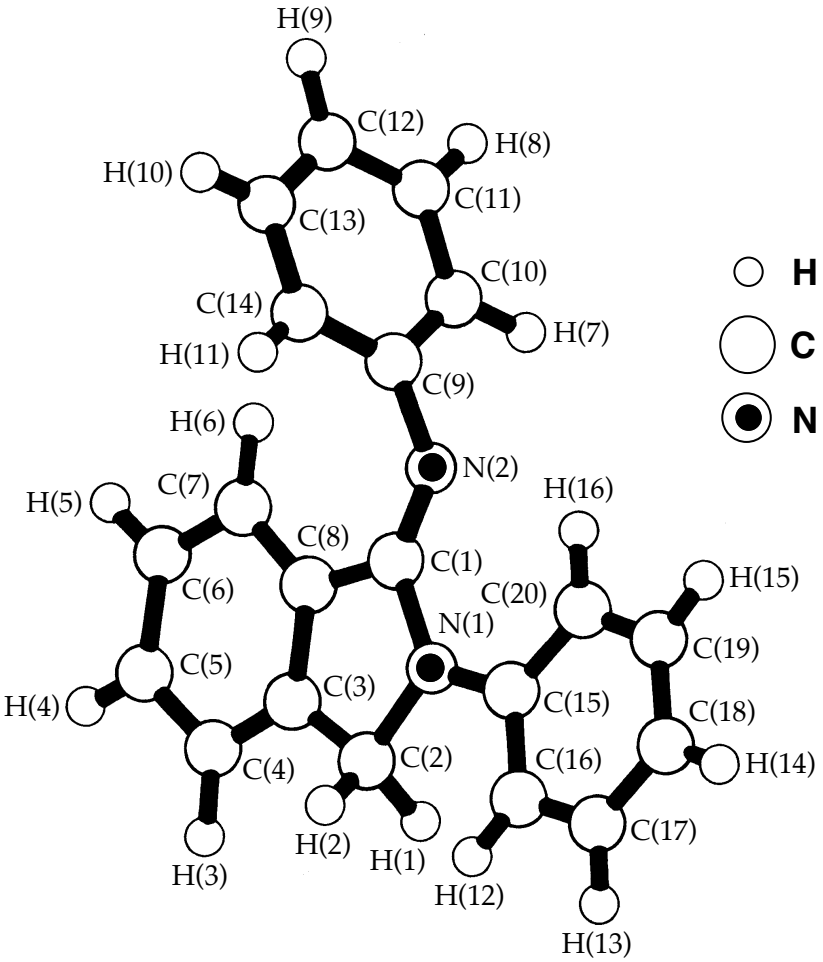


Figure 1

REFERENCES AND NOTES

1. Part 11: I. Takahashi, M. Tsuzuki, H. Kitajima, M. Hatanaka, S. Maeda, A. Yamano, T. Ohta, and H. Hosoi, *Anal. Sci.*, 2003, **19**, 973.
2. I. Takahashi and M. Hatanaka, *Heterocycles*, 1997, **45**, 2475.
3. N. G. Kundu, M. W. Khan, and R. Mukhopadhyay, *J. Indian Chem. Soc.*, 2001, **78**, 671.
4. I. Takahashi, T. Kawakami, E. Hirano, H. Yokota, and H. Kitajima, *Synlett*, 1996, 353; I. Takahashi, T. Kawakami, M. Kimino, E. Hirano, S. Kamimura, T. Tamura, H. Kitajima, M. Hatanaka, H. Uchida, A. Nomura, and M. Tanaka, *Heterocycles*, 2001, **54**, 635.
5. S. M. Allin, C. C. Hodkinson, and N. Taj, *Synlett*, 1996, 781.
6. T. Kametani, K. Kigasawa, M. Hiiragi, H. Ishimaru, S. Haga, and K. Shirayama, *J. Heterocycl. Chem.*, 1978, **15**, 369.
7. I. Takahashi, K. Takeuchi, A. Yoshida, and H. Kitajima, *Mem. Cryogen. Lab., Fukui Univ.*, 1996, **9**, 53.
8. A single crystal of **4** for an *X*-Ray analysis was obtained by slow evaporation of diethyl ether solution (mp 184-185 °C). *X*-Ray crystal data for **4** ($C_{20}H_{16}N_2$): Rigaku AFC5R diffractometer, Cu K_α (λ = 1.54178 Å), crystal dimensions 0.10x0.10x0.50 mm^3 (lemon yellow prism), a = 5.4114(8), b = 20.922(2), c = 13.034(2) Å, β = 92.32(1)°, monoclinic space group $P2_1/n$ (No.14), T = 23 °C, Z = 4, μ(Cu K_α) = 5.5 cm^{-1}, M_r = 286.36, V = 1474.4(3) $Å^3$, anode power = 12 kW, D_{calc} = 1.281 g/cm^3, $2\theta_{max}$ = 120.2°, F(000) = 600; of 2542 reflections measured, 1712 were observed ($I > 3.00\ \sigma(I)$), number of parameters = 263. The structure was solved by a direct method and was refined on Mithril (cf. C. J. Gilmore, *J. Appl. Cryst.*, 1984, **17**, 42). Data were corrected for Lorentz polarizations. The data/parameter ratio was 9.67. R = 0.044, R_W = 0.070, GOF = 1.29, max/min residual density = +0.16/-0.26 $eÅ^{-3}$. All calculations were performed using the TEXSAN Crystallographic Structure Analysis Package of the Molecular Structure Corporation (Woodlands, TX, USA, 1985). Crystallographic data (excluding structure factor) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-225617. Copies of the data can be obtained free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: (+44)223-33603; e-mail: deposit@ccdc.cam.ac.uk].
9. I. Takahashi, *Mem. Fac. Eng., Fukui Univ.*, 1996, **44**, 425.