

Reaction Systems Peripheral to the 1:2 Mannich Condensation Reaction between *o*-Phthalaldehyde and Primary Amine

I. Takahashi^{*a}, K. Nishiuchi^a, R. Miyamoto^a, M. Hatanaka^a, H. Uchida^a, K. Isa^b, A. Sakushima^c and S. Hosoi^c

^aDepartment of Applied Chemistry and Biotechnology, Faculty of Engineering, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8507, Japan

^bFaculty of Education and Regional Studies, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8507, Japan

^cDepartment of Pharmacognosy and Chemistry of Natural Products, School of Pharmaceutical Sciences, Kyushu University of Health and Welfare, 1714-1 Yoshino-cho, Nobeoka 882-8508, Japan

Received May 27, 2004; Accepted July 1, 2004

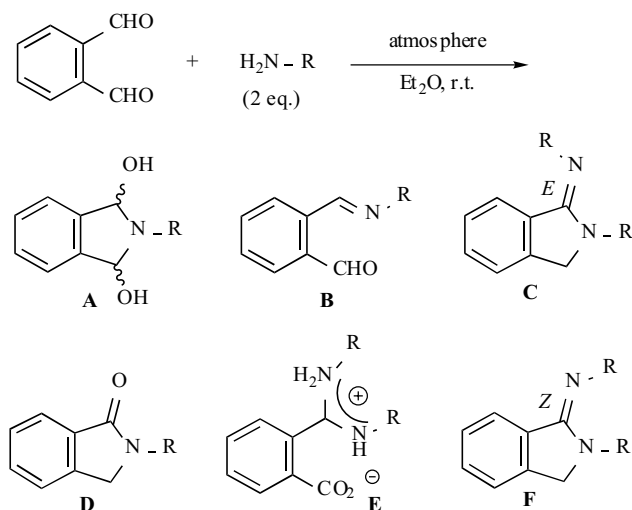
Abstract: Reaction systems peripheral to the 1:2 condensation reaction between *o*-phthalaldehyde and primary amine were studied. Newly identified were 1,3-dihydroxyisoindoline, *o*-iminomethylbenzaldehyde and *o*-amidiniobenzoate, the last of which exhibited moderate anticancer activity.

Keywords: 1,3-dihydroxyisoindoline, *o*-iminomethylbenzaldehyde, *o*-amidiniobenzoate, anticancer activity.

Heterocyclic molecules possessing phthalimidine (2,3-dihydroisoindol-1-one) skeletons have attracted considerable synthetic interests in recent years, as a number of fascinating natural/artificial bioactive compounds such as staurosporine (protein kinase C inhibitor), indoprofen (*anti*-inflammatory agent), and DN-2327 (also known as pazinaclone; anxiolytic agent) have shown clinical utility [1,2]. We have previously reported the 1:2 condensation reaction between *o*-phthalaldehyde (OPT) and substituted aniline as the re-examination of the Kametani phthalimidine synthesis to afford (*E*)-2-aryl-1-(*N*-arylimino)-isoindolines [3], instead of previously reported diimines [4]. It was found in the synthesis that when *p*-toluidine is used as substituted aniline, a curious phenomenon is encountered. Thus, 2-(*p*-tolyl)-1-(*N*-(*p*-tolyl)imino)isoindoline, the product at a reaction time of 4 h, changes into a different material, which is moderately soluble in CDCl₃ when the reaction time is prolonged. These findings encouraged us to carry out a systematic study of the reaction system peripheral to "Kametani condensation", the results of which we report herein.

General experimental procedure: *o*-phthalaldehyde (OPT) was added portionwise to a solution of amine [2 molar equiv.; used were 2 mole of monoamine (Runs 1-17), 1 mole of diamine (Runs 18-20), or 1 mole each of two different monoamines (Run 21)] in diethyl ether (and small quantity of DMF if necessary), and the mixture was stirred at room temperature under an appropriate atmospheric condition. Precipitates formed in due course were filtered, washed with small quantity of ice-cold diethyl ether, and then dried *in vacuo*. Product distribution patterns were calculated from ¹H NMR spectra. Results are summarized in Table 1.

*Address correspondence to this author at the Department of Applied Chemistry and Biotechnology, Faculty of Engineering, University of Fukui, 3-9-1 Bunkyo, Fukui 910-8507, Japan; Tel.: +81-776-27-8761; Fax: +81-776-27-8747; E-mail: ichiro@acbio2.acbio.fukui-u.ac.jp



Scheme 1.

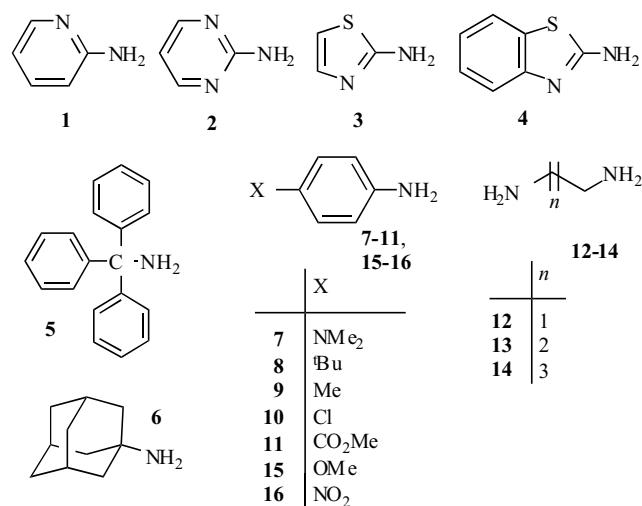


Chart 1.

Table 1. Product Distribution Patterns in the Condensation Reaction [a]

Run	Amine		Et ₂ O (mL)	Atmosphere[e]	Time(h)	Isolated Yield (%)					
	Compd.	mmol				A	B	C	D	E	F
1	1	10	25	open	4	86	----	----	----	----	----
2	1	10	25[c]	open	24	40	----	----	----	----	----
3	2	10	15	open	24	40	----	----	----	----	----
4	3	10	25	open	4	96	----	----	----	----	----
5	4	10	25	open	24	97	----	----	----	----	----
6	5	2.3	15	open	24	----	50	----	----	----	----
7	6	10	35	open	24	----	----	24	32	----	----
8	7	10	25	Ar	24	----	----	71	12	----	----
9	8	10	25	Ar	24	----	----	40	40	----	----
10[b]	9	10	10	Ar	24	----	----	34	----	----	----
11[b]	10	10	19	open	48	----	----	59	----	----	----
12[b]	11	10	25[d]	Ar	24	----	----	62	----	----	----
13	9	10	10	open	4	----	----	21	----	----	----
14	9	10	20	open	24	----	----	----	----	55	----
15	9	10	10	O ₂	24	----	----	----	----	55	----
16	10	10	10	O ₂	24	----	----	46	----	5	----
17	11	10	10	O ₂	24	----	----	69	----	----	----
18	12	5	25	open	24	----	----	----	----	----	40[f]
19	13	5	25	open	24	----	----	----	----	----	51[g]
20	14	5	25	open	24	----	----	----	----	----	36[h]
21	15+16	5+5	25	open	24	----	----	----	----	----	30[i]

[a] Reactions between OPT and amine were carried out in 1:2 molar ratio. [b] Ref. 3. [c], [d] DMF was added to the reaction system (5 and 1 mL, respectively). [e] Runs indicated by "open" were carried out using glasswares equipped with dried tubes on top; Ar & O₂ with balloons. [f]-[i] Structures are given as 17-20, respectively.

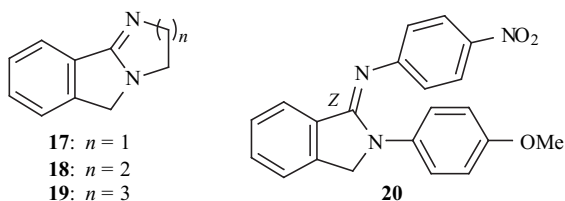


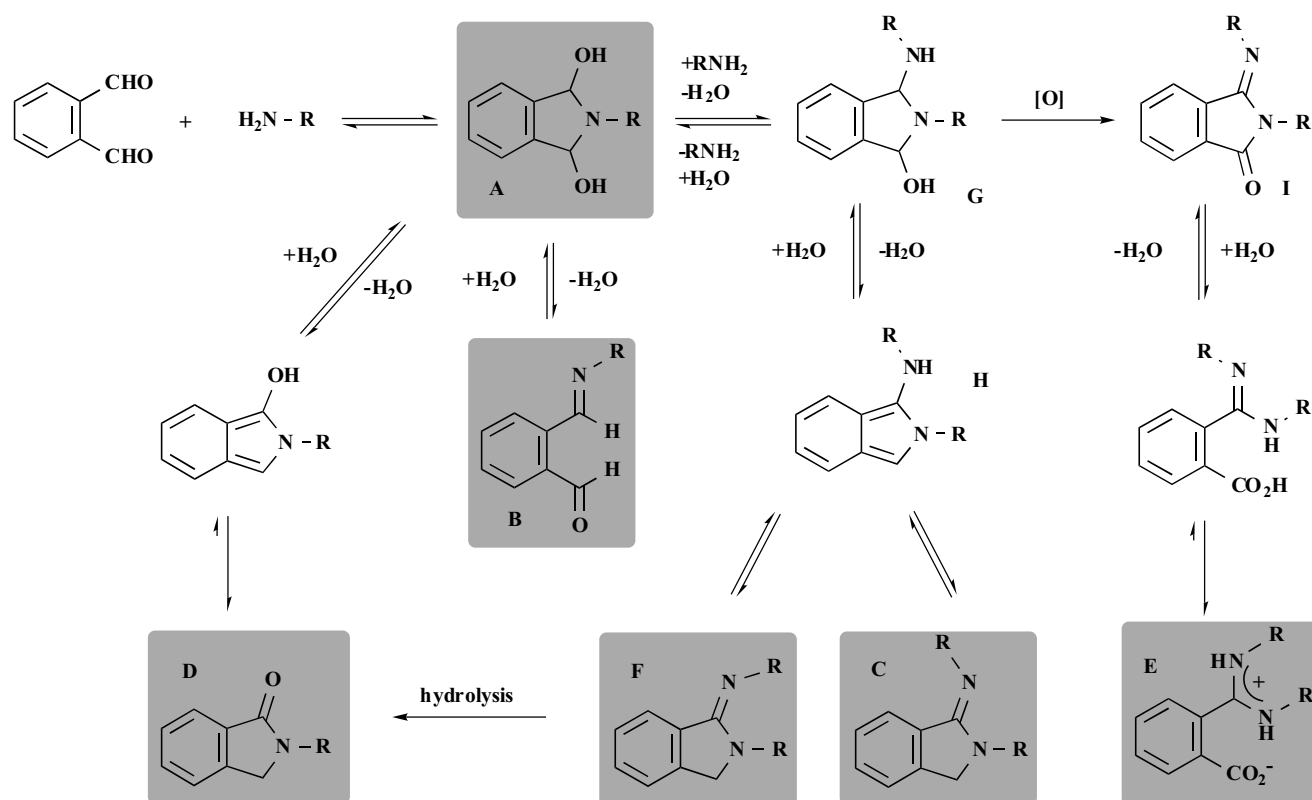
Chart 2.

Characteristic observations in this series of reactions are as follows:

- When the amine possessed the heteroatom at the 2-position (1-4), the reaction was interrupted as soon as 1,3-dihydroxyisoindoline (A; 1:1 addition product between OPT and amine) was formed (Runs 1 and 3-5). The addition of DMF to the reaction system merely intervened in the precipitation of A (Run 2).
- When the amine had a bulky substituent, diverse features were found: (a) when tritylamine (5) was used, the only identifiable product was monoimine (B; Run 6); (b) when 1-adamantylamine (6) was

used, together with ordinary (*E*)-iminoisoindoline (C), the corresponding phthalimidine (D) was formed (Run 7).

- In the examination using a series of aniline derivatives (7-11), we have previously reported the results using 9-11 (Runs 10-12) [3]. Except for the cases of *p*-(*N,N*-dimethylamino)aniline (7) and *p*-*tert*-butylaniline (8) in which phthalimidines (D) were formed as by-products (Runs 8 and 9), (*E*)-iminoisoindolines (C) were formed in fair to good isolated yields (Runs 10-12).
- In cases where *p*-toluidine (9) was used as an amine, to our astonishment, product distribution patterns were found to be effected dramatically by atmospheric conditions. Thus, under "open" conditions, the 4-h reaction (Run 13) gave (*E*)-iminoisoindoline (C), whereas the 24-h reaction gave an amino-acid (E; innersalt form) as a sole product (Run 14) [5]. The result from Run 15, in which the reaction was carried out under oxygen atmosphere, enabled us to attribute



Scheme 2.

the cause to aerial oxygen. In addition, the presence of electron-withdrawing group diminished the effect (Runs 16 and 17), suggesting that the intermediary process may include the generation of radical cation species.

- (5) The use of appropriate diamines (**12-14**) gave cyclized products (**17-19**; Runs 18-20), which belong to the (*Z*)-series of iminoisoindolines (**F**). Interestingly, open-chain type compound (**20**) of class **F** was obtained, merely starting the reaction from a mixture of amines (Run 21) [6].

Based on the experimental results described above, a plausible reaction path can be depicted as Scheme 2.

Thus, from the 1:1 addition of OPT with a first mole of amine, 1,3-dihydroisoindolinol (**A**) is formed first. Dehydration of **A** affords monoimine (**B**), however, the isolation of which has been rare in our past experiences; in the case of Run 6 in the present study, **B** happens to be poorly soluble, which would shift the equilibrium toward dehydration. Further condensation of **A** with a second mole of amine affords a 1-amino-3-isoindolinol intermediate (**G**; similar type of compounds were obtained in our previous studies using benzotriazole as a synthetic auxiliary) [7,8]. Dehydration of this intermediate gives aminoisoindole (**H**), which quickly tautomerizes to afford energetically feasible iminoisoindolines (**C** and **F**) [9,10]. According to our preliminary results with PM3 calculations [11], **F** [(*Z*)-form] was energetically more favorable (*ca.* 1 kcal/mol) than **C** [(*E*)-form], and therefore, the preferentially obtainable **C** [3] is considered as a kinetic product. Formation of phthalimidine (**D**) can be explained either by simple dehydration of **A** (known as Thiele's method [12]) or

hydrolysis of **F**; the latter, which scarcely happens in our experiences, would be made possible by some steric hindrance-induced skew of 1-imino group from the isoindole plane.

On the other hand, amino acid inner salt (**E**) is likely to cyclize to give iminophthalimidine (**I**) under acidic conditions, as has been proved from ¹H NMR spectra in trifluoroacetic acid-*d* (TFAD). We have not been successful in the isolation of compound **I** for the present [13], but still, we are convinced that the single-electron type oxidation (induced by aerial oxygen) of **G** should give **I**, as reported by Nan'ya and co-workers in the reaction system related to our present study [14,15]; compound **I** is expected to be hydrolyzed by water in the reaction system followed by proton migration to give compound **E**, the revert process of which is proven.

Intriguingly, inner salt (**E**) obtained from Run 16, though in low yield (only 5 %), exhibited moderate anticancer activity against L1210 and KB (IC₅₀ = 33.1 and 29.7 μg/mL, respectively) [16]. Further investigation of the inner salt formation reaction path is currently underway.

ACKNOWLEDGEMENTS

Authors are grateful to Professor K. Görlitzer (TU Braunschweig) for his provision of isoindole-related useful information.

REFERENCES AND NOTES

- [1] Takahashi, I.; Hatanaka, M. *Heterocycles*, **1997**, *45*, 2475.
- [2] Kundu, N. G.; Khan, M. W.; Mukhopadhyay, R. *J. Indian Chem. Soc.*, **2001**, *78*, 671.

- [3] Takahashi, I.; Miyamoto, R.; Nishiuchi, K.; Hatanaka, M.; Yamano, A.; Sakushima, A.; Hosoi, S. *Heterocycles*, **2004**, *63*, 1267.
- [4] Kametani, T.; Kigasawa, K.; Hiiragi, M.; Ishimaru, H.; Haga, S.; Shirayama, K. *J. Heterocycl. Chem.*, **1978**, *15*, 369.
- [5] Structures of compounds belonging to class E were characterized by ¹H NMR spectra and combustion analyses.
- [6] Structure of **20** was determined by MS and ¹H NMR spectra. In the latter, assignments of aryl groups derived from anilines were done by comparison with spectra of compounds of class C (R = *p*-MeOC₆H₄- and *p*-NO₂-C₆H₄-). The (*Z*)-isomerism was supported by the presence of H-7 proton, which was *ca.* 0.8 ppm less shielded than that of (*E*)-isomer.
- [7] Takahashi, I.; Tsuzuki, M.; Yokota, H.; Kitajima, H.; Isa, K. *Heterocycles*, **1994**, *37*, 933.
- [8] Takahashi, I.; Tsuzuki, M.; Yokota, H.; Morita, T.; Kitajima, H.; Isa, K. *Heterocycles*, **1996**, *43*, 71.
- [9] Görlitzer, K. *Arch. Pharm. (Weinheim)*, **1976**, *309*, 356.
- [10] Görlitzer, K.; Duß, D. *Arch. Pharm. (Weinheim)*, **1985**, *318*, 735.
- [11] The PM3 calculations of iminoisoindolines (**C** and **F**; R = *p*-MeOC₆H₄- and *p*-AcC₆H₄-) were performed with the MOPAC-PM3 program implemented in the CAChe ver. 6.0 for Apple Macintosh; Fujitsu Co. Ltd.; Chiba, Japan.
- [12] Thiele, J.; Schneider, J. *Ann. Chem.*, **1909**, *369*, 287.
- [13] All attempts in the isolation of compound **I** in the "forward" path (**A** to **E**) were unsuccessful. When drying agents such as MS4A or MgSO₄ were used, the product turned out to be a mixture of polymeric materials. Similar trends were found in our previous studies. *Cf.* Takahashi, I.; Tsuzuki, M.; Yokota, H.; Morita, T.; Kitajima, H. *Heterocycles*, **1996**, *43*, 71.
- [14] Nan'ya, S.; Tange, T.; Maekawa, E. *J. Heterocycl. Chem.*, **1985**, *22*, 449.
- [15] Nan'ya, S.; Ishida, H.; Batsugan, Y. *J. Heterocycl. Chem.*, **1994**, *31*, 1725.
- [16] Amino acid innersalt (**E**) possessing other substituents such as in Run 15 exhibited weak anticancer activities (IC₅₀ > 100 µg/mL).