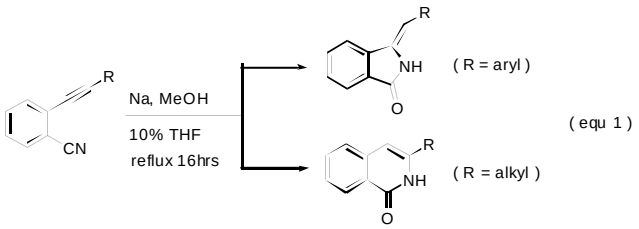
Solvent Effects on Aza-anionic Cycloaromatization of 2-(2-Substituted-ethynyl)benzonitriles

Chi-Fong Lin (林志峰), Jia-Huei Yang (楊嘉惠), Pei-Chen Hsieh (謝佩珍), Wen-Der Lu (盧文德) and Ming-Jung Wu* (吳明忠)
School of Chemistry, Kaohsiung Medical University, Kaohsiung, Taiwan

The methanolysis of 2-(2-arylethynyl)benzonitriles is accelerated when the polar aprotic solvents are added, which could enhance the 6-endo pathway and give isoquinolones, though the 5-exo pathway is occupied mostly. The yields of products would also be increased.

The biradical cycloaromatization of enediynes have attracted extensive attention,[1] and enormous effort has been poured into elucidating the biological modes of action of these novel natural products.[2] The synthesis of natural enediynes[3] and the development of simplified synthetic analogues[4] have also been pursued in earnest. However, many reactions in which enediynes could proceed still remain unsolved.

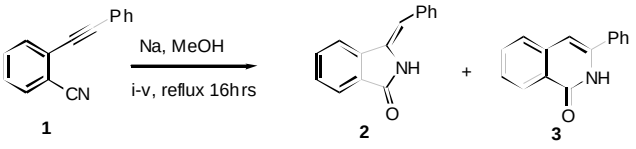
We have previously reported an ionic cycloaromatization of 2-(2-substituted-ethynyl)benzonitriles[5] to give the 3-benzylideneisoindol-2-ones (equ. 1) in modest yield. It is considered that the low yield could be due to the poor regioselectivity of the nucleophilic addition to the conjugate system. We then anticipated that introducing a polar aprotic solvent could increase the nucleophilicity of nucleophile which would promote the cycloaromatization of 2-(2-substituted-ethynyl)benzonitriles in better yields and regioselectivity.



(equ 1)

Our first attempt was carried out by mixing 2-(2-phenylethynyl)benzonitrile **1** with sodium methoxide in methanol containing 10% THF, and the reaction mixture was refluxed for 16 hrs. After the usual workup and chromatography, compound **2** was obtained in 88% yield. Various percentages and polar aprotic solvents were then employed in the same reaction. The results are summarized in Table 1. When the amount of THF was increased to 30%, isoindolone **2** was obtained in 65% yield along with 7% yield of isoquinolone **3**. In

Table 1.



1 **2** **3**

additive		yield	
i	10% THF	88%	
ii	30%THF	56%	7%
iii	10%DMF	no reaction	
iv	10%DMSO	50%	12%
v	30%DMSO	45%	17%

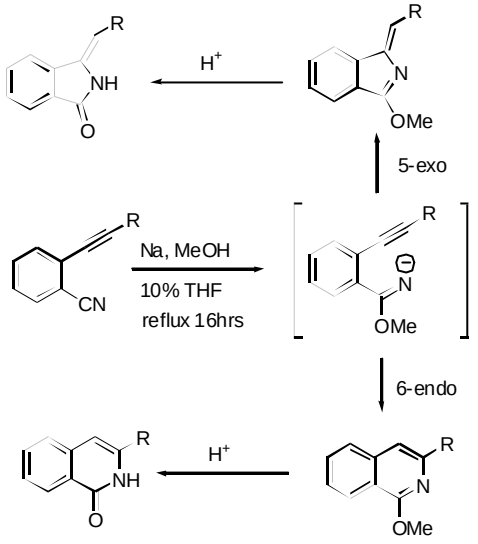
the 10% DMF condition, no expected reaction occurred, which perhaps is owing to the reaction between sodium methoxide and DMF. On the other hand, when either 10% or 30% DMSO was mingled, either isoindolone **2** or isoquinolone **3** were obtained. The isoqunolone **3** could not be separated from isoindolone **2** by column chromatography; it would only be observed from the NMR spectrum.

The appearance of isoquinolone **3** was unexpected, which suggested that when the amount of polar aprotic solvent was increased, the regioselectivity of the reaction would be lowered. It revealed that the energy difference of the transition states between 6-endo and 5-exo pathway would be lessened, although the 5-exo pathway was mostly occupied (Scheme I).

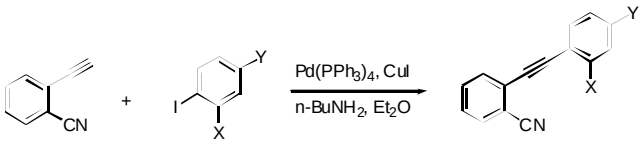
Preparation of 2-(2-arylethynyl)benzonitriles **9-12** were accomplished by the direct palladium-catalyzed coupling reaction of 2-ethynylbenzonitrile **4** with aryl iodides **5-8** (Scheme II). Compounds **9-12** were then heated to reflux with sodium methoxide in methanol containing 10% THF, respectively. The results are summarized in Scheme III.

When the aryl group had the electron-donating group at

Scheme I



Scheme II



4

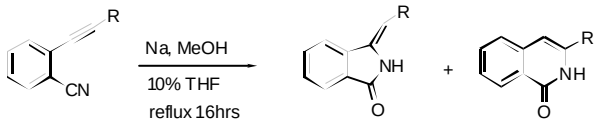
5 X= H, Y= CH_3 — **9** (69%)

6 X= H, Y= OCH_3 — **10** (45%)

7 X= OCH_3, Y= H — **11** (48%)

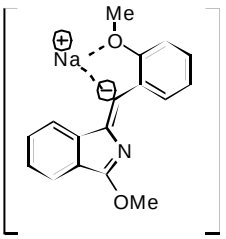
8 X= CF_3, Y= H — **12** (55%)

Scheme III



9	R = p-CH_3-C_6H_4	**9a** (67%)	**9b** (12%)
10	R = p-CH_3O-C_6H_4	**10a** (45%)	**10b** (7%)
11	R = o-CH_3O-C_6H_4	**11a** (94%)	
12	R = o-CF_3-C_6H_4	**12a** (65%)	

the para-position, both isoindolone and isoquinolone products were observed. However, cyclization of 2-(2-(2-methoxyphenyl)ethynyl)benzonitrile **11** gave the isoindolone **11a** in 94% yield as the only product. This could be due to the extra stabilization of the 5-exo cyclization intermediate **I** by the coordination of oxygen with sodium.



I

There are several significant points arising from this study including the following: (1) The anionic cycloaromatization of 2-(2-arylethynyl)benzonitriles would be promoted by adding polar aprotic solvents. (2) The generation of 6-endo products explored a novel reaction mode of the aza-anionic cycloaromatization of enediynes. (3) The yields of cyclized products were augmented,[5] while polar aprotic solvents were added; as the amount of aprotic solvents were increased, the yield of 6-endo products were also increased.

EXPERIMENTAL SECTION

General Procedure for Coupling of 2-Ethynylbenzonitrile with Aryl Iodide

To a degassed solution of 2-ethynylbenzonitrile (1 mmol) in dry ether (20 mL) containing CuI (0.03 g, 0.15 mmol), n-$BuNH_2$ (0.2 g, 0.25 mmol) was added a degassed solution of aryl iodide (1.2 mmol) containing $Pd(PPh_3)_4$ (0.03 g, 0.15 mmol) in dry ether (10 mL). The reaction mixture was stirred for 6 hrs and quenched with sat. NH_4Cl(aq). The aqueous layer was extracted with EtOAc (30 mL*3) and the combined organic layers were washed with sat. $NaHCO_3$(aq) and dried over anhydrous $MgSO_4$(s). After filtration and removal of solvent *in vacuo*, the residue was purified by column chromatography to give the sole products.

2-(2-(4-Methyl)phenyl)ethynyl)benzonitrile (9)[5]

Obtained in 69% as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.68~7.49 (m, 5H), 7.39 (td, 1H, J = 7.8, 2.0 Hz), 7.18 (d, 2H, J = 8.0 Hz), 2.38 (s, 3H).

2-(2-(4-Methoxy)phenyl)ethynyl)benzonitrile (10)[6]

Obtained in 45% as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.69~7.51 (m, 5H), 7.38 (td, 1H, J = 7.8, 2.0 Hz), 6.89 (dd, 2H, J = 7.8, 2.0 Hz), 3.83 (s, 3H), ^{13}C NMR ($CDCl_3$,

50 MHz) δ 160.4, 133.6, 132.6, 132.3, 132.1, 131.8, 127.8, 127.7, 117.7, 115.1, 114.1, 96.4, 84.6, 55.3.

2-(2-(2-Methoxy)phenyl)ethynyl)benzonitrile (11)[6]

Ob tained in 48% as a yel low oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.67~7.64 (m, 2H), 7.59~7.53 (m, 2H), 6.97~6.91 (m, 2H), 3.94 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 160.4, 133.9, 132.6, 132.2, 132.1, 130.8, 127.9, 127.6, 120.5, 117.6, 115.2, 111.4, 110.8, 92.7, 89.5, 55.8.

2-(2-(2-Trifluoromethyl)phenyl)ethynyl)benzonitrile (12)[6]

Ob tained in 55% as a col or less oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.80 (d, 1H, *J* = 8.0 Hz), 7.73~7.59 (m, 4H), 7.56~7.41 (m, 3H).

General Procedure for Methanolysis of 2-Alkynyl-benzonitrile

To a so lu tion of 2-alkynylbenzonitrile (1 mmol) in 10 mL of methanol was added freshly cut sodium metal (5 mmol); the so lu tion was heated to re flux and stirred for 16 hr. After cool ing to room tem per a ture, the meth a nol was re-moved *in vacuo*. To the res i due, sat NaCl (aq) was added and ex tracted with EtOAc. The com bined or ganic layer was dried over an hy drous $MgSO_4$(s). Af ter fil tra tion and re moval of sol vent, the res i due was pu ri fied by col umn chro ma tog ra phy to give the sole prod ucts.

3-(4-Methylbenzylidene)isoindol-1-one (9a)[5] and 3-(4-Methylphenyl)isoquinolin-1-one (9b)

Ob tained in 79% as a white solid, from ^{1}H NMR spec-trum, it shows as a mix ture of **9a** (67%) and **9b** (12%). The fol low ing peaks of spec trum be long to **9a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.18 (bs, 1H), 7.88 (dt, 2H, *J* = 8.0, 0.8 Hz), 7.63 (td, 1H, *J* = 6.6, 1.2 Hz), 7.51 (td, 1H, *J* = 6.6, 1.2 Hz), 7.35 (d, 2H, *J* = 8.0 Hz), 7.25 (d, 2H, *J* = 8.0 Hz), 6.53 (s, 1H), 2.39 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.8, 137.8, 132.4, 132.2, 132.1, 129.9, 129.0, 128.3, 123.5, 119.7, 106.0, 21.3. The following peaks of spectrum belong to **9b**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.71 (bs, 0.2H), 6.83 (s, 0.2H), 2.45 (s, 0.6H); the other peaks of ar o matic could not be sep a rated from **9a**.

3-(4-Methoxybenzylidene)isoindol-1-one (10a)[7] and 3-(4-Methoxyphenyl)isoquinolin-1-one (10b)

10a and **10b** ob tained in 52% as a yel low solid, from ^{1}H NMR spec trum, it shows as a mix ture of **10a** (45%) and **10b** (7%). The following spectrum belong to **10a**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.15 (bs, 1H), 7.87 (dd, 1H, *J* = 7.6, 1.2 Hz), 7.77 (dd, 1H, *J* = 7.6, 1.2 Hz), 7.62 (td, 1H, *J* = 7.6, 1.2 Hz), 7.49 (td, 1H, *J* = 7.6, 1.2 Hz), 7.39 (dd, 2H, *J* = 7.4, 2.0 Hz), 6.97 (dd, 2H, *J* = 7.4, 2.0 Hz), 6.52 (s, 1H), 3.86 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.9, 159.2, 138.2, 132.2, 131.7, 129.8, 128.9, 127.5, 123.6, 119.6, 114.8, 105.9, 55.4. The fol low ing peaks of spec trum be long to **10b**. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.37 (bs, 0.16H), 6.72 (s, 0.16H), 3.87 (s, 0.5H), the other peaks of ar o matic could not be sep a rated from **10a**.

3-(2-Methoxybenzylidene)isodol-1-one (11a)[8]

Ob tained in 94% as a yel low solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.33 (bs, 1H), 7.84 (t, 2H, *J* = 8.4 Hz), 7.62 (td, 1H, *J* = 7.4, 1.4 Hz), 7.51 (dd, 1H, *J* = 7.4, 1.4 Hz), 7.46~7.27 (m, 2H), 7.06~6.95 (m, 2H), 6.63 (s, 1H), 3.93 (s, 3H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ 168.5, 156.4, 138.4, 132.9, 132.0, 130.4, 130.3, 129.4, 128.9, 123.8, 123.5, 121.4, 119.9, 111.6, 102.3, 55.8; mp = 196-197 °C.

3-(2-Trifluoromethylbenzylidene)isoindol-1-one (12a)

Ob tained in 65% as a white solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.89 (dd, 1H, *J* = 3.6, 0.4 Hz), 7.84 (dd, 1H, *J* = 3.6, 0.4 Hz), 7.76 (d, 1H, *J* = 4.2 Hz), 7.68 (td, 1H, *J* = 3.6, 0.4 Hz), 7.63~7.44 (m, 3H), 7.48~7.42 (m, 1H), 6.76 (s, 1H); mp = 206-207 °C.

ACKNOWLEDGMENT

We would like to thank the Na tional Sci ence Coun cil of the Re pub lic of China for fi nan cial sup port.

Received October 19, 2000.

Key Words

Enediyne; Methanolysis; Regioselectivity; Anionic cycloaromatization.

REFERENCES

1. (a) Wendi, M. D.; Kerwin, S. M. *J. Am. Chem. Soc*. **1997**, *119*, 1464. (b) Shi, C. S.; Wang, K. K. *J. Org. Chem.* **1998**, *63*, 3517. (c) Wu, M. J.; Lin, C. F.; Wu, J. S.; Chen, H. T. *TetrahedronLett*. **1994**, *35*, 1879.
2. Nicolaou, K. C.; Dai, W. M. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1387.
3. (a) Nicolaou, K. C. *Angew. Chem. Int. Ed. Engl*. **1993**, *32*, 1377. (b) Hichcock, S. A.; Boyer, S. H.; Chu-Moyer, M.

Y.; Olson, S. H.; Denishesky, S. D. *Angew. Chem. Int. Ed. Engl*. **1994**, *33*, 858. (c) Meyer, A. G.; Fraley, M. E.; Tom, N. J.; Co hen, S. B.; Madar, D. J. *Chem. Biol*. **1995**, *2*, 33.

4. (a) Maier, M. E. *Synlett.* **1995**, 13. (b) Nicolaou, K. C.; Smith, A. L.; Yue, E. W. *Proc. Natl. Acad. Sci. U. S. A.* **1993**, *90*, 5881.
5. Wu, M. J.; Chang, L. J.; Wei, L. M.; Lin, C. F. *Tetrahedron* **1999**, *55*, 13193.
6. Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481.
7. Guillaume, J.; Boccara, N.; Demerseman, P.; Royer, R.; Bideau, J. P. *J. Heterocycl. Chem.* **1990**, *3*, 605.
8. Yoshiaki, K.; Masumi, T.; Kazuo, A. *Chem. Pharm. Bull.* **1993**, *11*, 2003.