HETEROCYCLES, Vol. 66, 2005, pp. 91 – 94. © The Japan Institute of Heterocyclic Chemistry
Received, 30th August, 2005, Accepted, 11th October, 2005, Published online, 14th October, 2005. COM-05-S(K)35

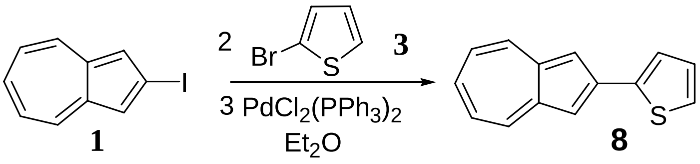
THE SYNTHESIS OF HETEROARYLAZULENE

Taku Shoji,[a] Shigeru Kikuchi,[b] Shunji Ito,[c] and Noboru Morita[a]*

[a]*Department of Chemistry, Graduate School of Science, Tohoku University, Aoba-ku, Sendai 980-8578, Japan*
morita@funorg.chem.tohoku.ac.jp
[b]*Graduation School of Science and Technology, Kumamoto University, Kurokami 2-39-1, Kumamoto 860-8555, Japan*
[c]*Department of Material Science and Technology, Faculty of Science and Technology, Hirosaki University, Bunkyocho 3, Hirosaki 036-8561, Japan*

Abstract – Palladium-catalyzed cross-coupling reaction of 2- and 6-haloazulenes with lithium tri(heteroaryl)magnesates gave corresponding heteroarylazulenes in excellent yields which were independent of binding position.†

Heteroaryl compounds are utilized as important building blocks in materials science and supramolecular chemistry.[1] As part of our on going interest in a series of developing the methodology for polyfunctionalization of azulenes,[2] we have investigated the synthesis of heteroarylazulene by palladium-catalyzed cross-coupling reaction of 2- and 6-haloazulenes (**1**, **2**) with lithium tri(heteroaryl)magnesates which are easily prepared from commercially available bromothiophenes (**3**, **4**), bromopyridines (**5**, **6**),[3] and 3-bromoquinoline (**7**).[3] Establishment of general methodology for easily approach to heteroarylazulene from readily available materials is very difficult sometimes, because azulene resioisomers exhibit different character and the yields of reaction in azulene derivatives depend on binding position of the substituent. Pd-catalyzed cross-coupling reaction of haloazulenes with the heteroarylmagnesates gave corresponding heteroarylazulenes. As their high yields do not depend upon the binding position at C-2 and C-6 in azulene, we will report here.



Scheme 1

---

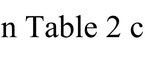
† This paper is dedicated to the memory of Dr. Kenji Koga, Emeritus Professor of Tokyo University.

Previously we report the preparation of azulenyllithium and magnesium reagents utilizing halogen-metal exchange reaction and their reactivities toward electrophiles.[4] Using this condition lithium tri(2-thienyl)magnesate[5] was prepared *in situ* and react with 2-iodoazulene as follows.

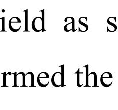
To a solution of *n*-butylmagnesium chloride (1.3 mL, 0.9 M solution in THF) in ether (10 mL) was added *n*-BuLi (1.5 mL, 1.6 M solution in hexane) at 0 ˚C. After it was stirred for 30 min at 0 ˚C, 2-bromothiophene (163 mg, 1.00 mmol) was added dropwise. The mixture was allowed to react at 0 ˚C for 1h. After a solution of 2-iodoazulene (254 mg, 1.00 mmol) and $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol) in ether (20 mL) was added dropwise at 0 ˚C, it was allowed to warm to room temperature and it was stirring for 24 h. The reaction was quenched with water. The product was isolated and purified by the usual way to afford 2,2'-thienylazulene (**8**, 198 mg, 0.942 mmol, 94%). The optimal condition Pd-catalytic amount was examined due to decrease catalytic amount as possible as low. To get a high yield, at least, 5 mol% of Pd-catalysis was needed as shown in Table 1.

Table 1. Relationship between amount of Pd-catalysis and yield

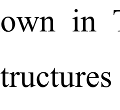
$PdCl_2(PPh_3)_2$	Yield	Recover
0 mol%	0	99
1 mol%	16	79
3 mol%	64	33
5 mol%	94	0



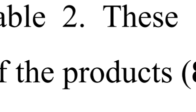
4



5

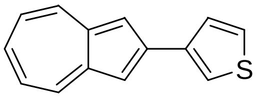


6

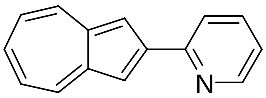


7

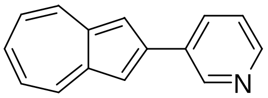
Another heteroarylmagnesates which were prepared *in situ* from compounds (**4**-**7**) gave corresponding heteroarylazulenes (**9**-**12**) in excellent yield as shown in Table 2. These ^{1}H NMR spectral data of heteroarylazulenes shown in Table 2 confirmed the structures of the products (**8**-**12**).



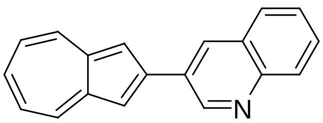
9



10



11

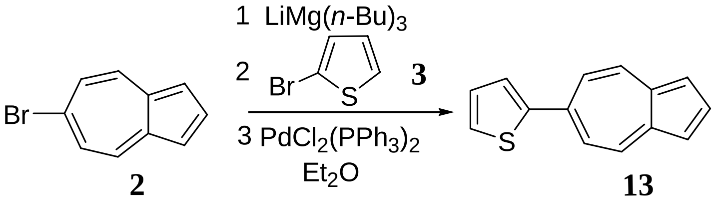


12

Table 2. Pd-catalyzed cross-coupling reaction of 2-iodoazulene with lithium tri(heteroaryl)magnesate

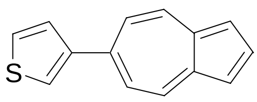
2-Heteroaryl-azulene	Yield	mp (˚C)	^{1}H NMR ($CDCl_3$)
8	94	143-144(dec.)	δ 8.22 (d, 2H, *J* =10. Hz, H-4,8), 7.58 (dd, 1H, *J* =4, 1.2 Hz, H-5'), 7.53 (s, 2H, H-1,3), 7.47 (t, 1H, *J* =10 Hz, H-6), 7.36 (dd, 1H, *J* =4, 1.2 Hz, H-3'), 7.14 (t, 2H, *J* =10. Hz, H-5,7), 7.13 (dd, 1H, *J* =4, 1.2 Hz, H-4')
9	96	132-133(dec.)	δ 8.25 (d, 2H, *J* =10. Hz, H-4,8), 7.77 (d, 1H, *J* =0.8 Hz, H-2'), 7.62 (dd, 1H, *J* =4.8, 0.8 Hz, H-4'), 7.55 (s, 2H, H-1,3), 7.48 (t, 1H, *J* =10 Hz, H-6), 7.41 (dd, 1H, *J* =4.8, 0.8 Hz, H-5'), 7.14 (t, 2H, *J* = 10 Hz, H-5,7)
10	99	114.5-115.0	δ 8.74 (d, 1H, *J*=8 Hz, H-6'), 8.34 (d, 2H, *J* =10 Hz, H-4,8), 7.99 (dt, 1H, *J*=8, 1.2 Hz, H-3'), 7.97 (s, 2H, H-1,3), 7.48 (dt, 1H, *J*=8, 1.2 Hz, H-5'), 7.41 (t, 1H, *J* =10 Hz, H-6), 7.22 (dt, 1H, *J*=8, 1.2 Hz, H-4'), 7.16 (t, 2H, *J* =10 Hz, H-5,7)
11	72	155-158(dec.)	δ 9.21 (d, 1H, *J*=1.6 Hz, H-2'), 8.57 (dd, 1H, *J*=4.8, 1.6, H-6'), 8.32 (d, 2H, *J*=10 Hz, H-4,8), 8.18 (dt, 1H, *J*=8, 1.6 Hz, H-5'), 7.67 (s, 2H, H-1,3), 7.56 (t, 1H, *J*=10 Hz, H-6), 7.37 (dd, 1H, *J*=4.8, 1.6 Hz, H-4'), 7.19 (t, 2H, *J*=10 Hz, H-5,7)
12	80	184-185	δ 9.53 (d, 1H, *J*=2.4 Hz, H-2'), 8.62 (d, 1H, *J*=2.4 Hz, H-4'), 8.34 (d, 2H, *J*=10 Hz, H-4,8), 8.12 (d, 1H, *J*=8.4 Hz, H-8'), 7.90(d, 1H, *J*=8.4 Hz, H-5'), 7.81 (s, 2H, H-1,3), 7.69 (t, 1H, *J*=8.4 Hz, H-6'), 7.59 – 7.53 (m, 2H, H-6,7'), 7.25 (t, 2H, *J*=10 Hz, H-5,7)

6-Bromoazulene (**2**) reacted with lithium tri(2-thienyl)magnesate in a similar manner to 2-iodoazulene to give 6-(2'-thienyl)azulene (**13**) in 94% yield.

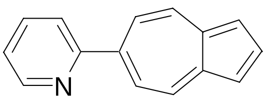


Scheme 2

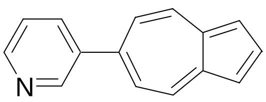
Another heteroarylmagnesates which were prepared *in situ* from compounds (**4-7**) also gave corresponding heteroarylazulenes (**14-17**) by Pd-catalyzed cross-coupling reactions in excellent yield as shown in Table 3. There are no large differences between the yields of 2-heteroarylazulenes and 6-heteroarylazulenes. These ^{1}H NMR spectral data of heteroarylazulenes as shown in Table 3 confirmed the structures of the products (**13-17**).



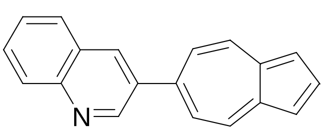
14



15



16



17

In summary, the large difference of their yields was not observed depend on the binding position. The yields are excellent. The heteroarylation of haloazulene by utilizing Pd-catalyzed lithium tri(heteroaryl) magnesate is one of the excellent methodologies for functionalization of azulene.

Table 3. Pd-catalyzed cross-coupling reaction of 6-bromoazulene with lithium tri(heteroaryl)magnesate

6-Heteroaryl-azulene	Yield	mp (˚C)	^{1}H NMR ($CDCl_3$)
13	94	160-161	δ 8.29 (d, 2H, *J*=10 Hz, H-4,8), 7.82 (t, 1H, *J*=4 Hz, H-2), 7.53 (d, 2H, *J*= 10 Hz, H-5,7), 7.47 (dd, 1H, *J*=4.4, 1.2 Hz, H-5'), 7.38 (dd, 1H, *J*=4.4, 1.2 Hz, H-3'), 7.34 (d, 2H, *J*=4 Hz, H-1,3), 7.11 (t, 1H, *J*=4.4 Hz, H-4')
14	98	180-181	δ 8.35 (d, 2H, *J* =10.8 Hz, H-4,8), 7.82 (t, 1H, *J* =4 Hz, H-2), 7.58 (dd, 1H, *J*=2.8, 1.6, H-2'), 7.49 – 7.41 (m, 4H, H-5,7,4',5'), 7.38 (d, 2H, *J* =4 Hz, H-1,3)
15	93	113.5-114.0	δ 8.75 (dd, 1H, *J* =4.8, 1.2 Hz, H-6'), 8.45 (d, 2H, *J*=10.8 Hz, H-4,8), 7.93 (t, 1H, *J*=4 Hz, H-2), 7.80 – 7.74 (m, 4H, H-5,7,3',5'), 7.41 (d, 2H, *J*=4 Hz, H-1,3), 7.28 (dt, 1H, *J*=4.8, 1.2, H-4')
16	70	119-120	δ 8.90 (d, 1H, *J*=2 Hz, H-2'), 8.65 (d, 2H, *J*=4.8 Hz, H-6'), 8.41 (d, 2H, *J*=10 Hz, H-4,8), 7.95 – 7.91 (m, 2H, H-2,5'), 7.45 (d, 2H, *J*=4 Hz, H-1,3), 7.39 (dd, *J*=8, 4.8 Hz, 1H, H-4'), 7.32 (d, 2H, *J*=10 Hz, H-5,7)
17	80	162-164	δ 9.22 (d, 1H, *J*=2 Hz, H-2'), 8.44 (d, 2H, *J*=10 Hz, H-4,8), 8.36 (s, 1H, H-4'), 8.17 (d, 1H, *J*=8 Hz, H-8'), 7.96 (t, 1H, *J*=4 Hz, H-2), 7.89 (d, 1H, *J*=8 Hz, H-5'), 7.76 (t, 1H, *J*=8 Hz, H-6'), .7.61 (d, 1H, *J*=8Hz, H-7'), 7.47 – 7.44 (m, 4H, H-1,3,5,7)

REFERENCES AND NOTES

1. A. R. Katritzky and C.W. Ress, 'In Comprehensive Heterocyclic Chemistry' Vol. 2, ed. by A. J. Boulton and A. McKillop, Pergamon Press, Inc., New York, 1984; R. E. Martin and F. Diederich, *Angew. Chem. Int. Ed.*, 1999, **38**, 1350; V. Balzani, A. Credi, F. M. Raymo, and J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2000, **39,** 3348.
2. We have already reported another several types of palladium-catalyzed coupling reactions which concern azulenes. See: R. Yokoyama, S. Ito, T. Okujima, T. Kubo, M. Yasunami, A. Tajiri, and N. Morita, *Trtrahedron*, 2003, **59**, 8191; S. Ito, H. Inabe, N. Morita, and A. Tajiri, *Eur. J. Org. Chem.*, **2004**, 1774; S. Ito, T. Terazono, T. Kubo, T. Okujima, N. Morita, T. Murafuji, Y. Sugihara, K. Fujimori, J. Kawakami, and A. Tajiri, *Tetrahedron*, 2004, **60**, 5357; S. Ito, T. Kubo, N. Morita, T. Ikoma, S. Tero-Kubota, J. Kawakami, and A. Tajiri, *J. Org. Chem.*, 2005, **70**, 2285; S. Ito, M. Ando, A. Nomura, N. Morita, C. Kabuto, H. Mukai, K. Ohta, J. Kawakami, A. Yoshizawa, and A. Tajiri, *J. Org. Chem.*, 2005, **70**, 3939.
3. S. Dumouchel, F. Mongin, F. Trécourt, and G. Quéguiner, *Tetrahedron*, 2003, **59**, 8629.
4. S. Ito, T. Kubo, N. Morita, Y. Matui, T. Watanabe, A. Ohta, K. Fujimori, T. Murafuji, Y. Sugihara, and A. Tajiri, *Tetrahedron Lett.,* 2004, **45**, 2891.
5. It can be also prepared directly from thiophene itself using lithium magnesate. O. Bayh, H. Awad, F. Mongin, C. Hoarau, F. Trécourt, G. Quéguiner, F. Blanco, B. Abarca, and R. Ballesteros, *Tetrahedron*, 2005, **61**, 4779.