Cycloaddition-based Formal C−H Alkynylation of Isoindoles Leading to the Synthesis of Air-stable Fluorescent 1,3-Dialkynylisoindoles

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ABSTRACT

Reaction of *N*-alkylisoindoles with (bromoethynyl)triisopropylsilane afforded 1,3-bis(triisopropylsilylethynyl) isoindoles in high yields. The formal C−H alkynylation proceeds under transition-metal-free conditions through [4 + 2] cycloaddition of the pyrrole ring of isoindole with bromoalkyne followed by ring-opening of the product.

Increasing effort has been devoted to the development of new aromatic and heteroaromatic compounds bearing alkynyl groups, because introduction of alkynyl groups often significantly changes their properties and stability. Indeed, aromatic compounds bearing two alkynyl groups on their aromatic ring have been used as high-performance electronic materials,[1] a component of molecular wires,[2] and starting substrates for conjugated polymers,[3] etc. For further exploration of new alkyne-conjugated functional molecules, it is highly desirable to find new aromatic core units along with their efficient synthesis.

We have focused on the synthesis and properties of isoindole derivatives, which are a less-explored motif in the development of organic materials, even though they generally show strong fluorescence.[4,5] One of the reasons for the limited attention is the lack of efficient reactions for direct functionalization of isoindoles.[4b,6] Recently, we established palladium-catalyzed C−H borylation and arylation of isoindoles for the synthesis of 1-boryl- and 1-arylisoindoles.[7] Based on the interesting reactivity of isoindoles in catalytic C−H functionalization,[7] as well as the recent great progress on a transition-metal-catalyzed C−H alkynylation of heterocyclic compounds,[8,9] we

(1) (a) Anthony, J. E. *Chem. Rev.* **2006**, *106*, 5028. (b) Anthony, J. E. *Angew. Chem., Int. Ed.* **2008**, *47*, 452.

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(4) For reviews on isoindole, see: (a) Jones, G. B.; Chapman, B. J. In *Comprehensive Heterocyclic Chemistry II*; Katrizky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol 2, p 1. (b) Donohoe, T. J. In *Science of Synthesis*; Thomas, E. J., Vol. Ed.; Georg Thieme Verlag: Stuttgart, 2000; Vol 10, p 653. (c) Heugebaert, T. S. A.; Roman, B. I.; Stevens, C. V. *Chem. Soc. Rev.* **2012**, *41*, 5626.

(5) For study on utilization of isoindoles as fluorescent and electroluminescent materials, see: (a) Zweig, A.; Metzler, G.; Maurer, A.; Roberts, B. G. *J. Am. Chem. Soc.* **1967**, *89*, 4091. (b) Ding, Y.; Hay, A. S. *J. Polm. Sci. Part A: Polym. Chem.* **1999**, *37*, 3293. (c) Gauvin, S.; Santerre, F.; Dodelet, J. P.; Ding, Y.; Hlil, A. R.; Hay, A. S.; Anderson, J.; Armstrong, N. R.; Gorjanc, T. C.; D'Iorio, M. *Thin Solid Films* **1999**, *353*, 218. (d) Mi, B.-X.; Wang, P.-F.; Liu, M.-W.; Kwong, H.-L.; Wong, N.-B.; Lee, C.-S.; Lee, S.-T. *Chem. Mater.* **2003**, *15*, 3148. (e) Jiao, L.; Yu, C.; Lin, M.; Wu, Y.; Cong, K.; Meng, T.; Wang, Y.; Hao, E. *J. Org. Chem.* **2010**, *75*, 6035. For study on isoindoles as bioactive molecules, see: (f) Diana, P.; Martorana, A.; Barraja, P.; Montalbano, A.; Carbone, A.; Cirrincione, G. *Tetrahedron* **2011**, *67*, 2072.

(6) For examples of electrophilic aromatic substitution reaction of isoindoles, see: (a) Winn, M.; Zaugg, H. E. *J. Org. Chem.* **1969**, *34*, 249. (b) Simons, S. S., Jr.; Ammon, H. L.; Doherty, R.; Johnson, D. F. *J. Org. Chem.* **1981**, *46*, 4739. (c) Bonnett, R.; North, S. A.; Newton, R. F.; Scopes, D. I. C. *Tetrahedron* **1983**, *39*, 1401. For nucleophilic substitution reaction of 1-haloisoindoles, see ref 5f.

(7) (a) Ohmura, T.; Kijima, A.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 6070. (b) Ohmura, T.; Kijima, A.; Suginome, M. *Org. Lett.* **2011**, *13*, 1238.

envisioned that C−H alkynylation would be useful for converting isoindoles to alkynylated isoindoles. Herein, we describe a synthesis of 1,3-dialkynylisoindoles via C−H alkynylation of isoindoles with 1-bromo-1-alkynes. It is interesting to note that the C−H alkynylation can be carried out under transition-metal-free conditions.[10]

During our studies on transition-metal-catalyzed C−H alkynylation of 2-methylisoindole (1a) with (bromoethynyl)-triisopropylsilane (2a), we performed the reaction in the absence of any transition metal catalyst at 110 °C (entry 1, Table 1).[11] We unexpectedly found formation of 1,3-bis-(triisopropylsilylethynyl)isoindole 3aa in 20% yield,[12] indicating that the C−H alkynylation of isoindole need no transition metal catalysts.[10] The yield of 3aa was improved to 85% when the reaction was carried out in the presence of K$_3$PO$_4$ (4 equiv) (entry 2). The C−H alkynylation of 1a also took place in the reaction of *tert*-butyldimethylsilyl-substituted alkyne 2b (entry 3). In sharp contrast, phenyl- and alkyl-substituted 2c−e did not give the C−H alkynyla-tion product 3c−e at all, but instead gave [4 + 2] cycloaddi-tion products 4c−e (entries 4−6).[11]

Bis(trialkylsilylethynyl)isoindoles 3aa and 3b showed remarkable stability under air, which is in sharp contrast to the relatively oxygen-sensitive isoindoles such as 1a and 1,3-diarylisoindoles.[13] Isoindoles 3aa and 3b could be purified by column chromatography on silica gel under air.

(8) For reviews on transition-metal-catalyzed C−H alkynylation of aromatic and heteroaromatic compounds, see: (a) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. (b) Messaoudi, S.; Brion, J.-D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 6495.

(9) For examples of transition-metal-catalyzed alkynylation of heterocyclic C(sp^2)−H bond, see: (a) Seregin, I., V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (b) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (c) Gu, Y.; Wang, X. *Tetrahedron Lett.* **2009**, *50*, 763. (d) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (e) Besselievre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (f) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512. (g) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868. (h) Yang, L.; Zhao, L.; Li, C.-J. *Chem. Commun.* **2010**, *46*, 4184. (i) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (j) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. (k) Berciano, B. P.; Lebrequier, S.; Besselievre, F.; Piguel, S. *Org. Lett.* **2010**, *12*, 4038. (l) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474. (m) Brand, J. P.; Waser, J. *Synthesis* **2012**, *44*, 1155. (n) Ackermann, L.; Kornhaass, C.; Zhu, Y. *Org. Lett.* **2012**, *14*, 1824. (o) Shibahara, F.; Dohke, Y.; Murai, T. *J. Org. Chem.* **2012**, *77*, 5381. (p) Brand, J. P.; Chevalley, C.; Scopelliti, R.; Waser, J. *Chem.—Eur. J.* **2012**, *18*, 5655. (q) Tolnai, G. L.; Ganss, S.; Brand, J. P.; Waser, J. *Org. Lett.* **2013**, *15*, 112.

(10) Although there have been some reports on transition-metal-free C−H alkynylation, these are limited to the reaction of pyrroles with 3-brormo-1-phenylprop-2-yn-1-one or ethyl 3-bromopropiolate. See: (a) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513. (b) Trofimov, B. A.; Sobenina, L. N.; Stepanova, Z. V.; Vakul'skaya, T. I.; Kazheva, O. N.; Aleksandrov, G. G.; Dyachenko, O. A.; Mikhaleva, A. I. *Tetra-hedron* **2008**, *64*, 5541 and references therein.

(11) The pyrrole ring of isoindole has been known as a reactive diene in [4 + 2] cycloaddition with dienophiles such as benzyne, dimethyl acetylenedicarboxylate, and N-methyl maleimide. For examples, see: (a) LeHoullier, C. S.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2364. (b) Chen, Z.; Müller, P.; Swager, T. M. *Org. Lett.* **2006**, *8*, 273. (c) Chen, Y.-L.; Lee, M.-H.; Wong, W.-Y.; Lee, A. W. M. *Synlett* **2006**, 2510. (d) Duan, S.; Sinha-Mahapatra, D. K.; Herndon, J. W. *Org. Lett.* **2008**, *10*, 1541. (e) Solé, D.; Serrano, O. *Org. Biomol. Chem.* **2009**, *7*, 3382. (f) Tong, B. M. K.; Hui, B.W.-Q.; Chua, S. H.; Chiba, S. *Synthesis* **2011**, 3552.

(12) The chemical structure of 3aa was confirmed by X-ray crystal-lographic analysis (see Supporting Information).

(13) For autooxidation of 1,3-diphenylisoindole, see: Ahmed, M.; Kricka, L. J.; Vernon, J. M. *J. Chem. Soc., Perkin 1* **1975**, 71.

Table 1. Reaction of Isoindole 1a with 1-Bromo-1-alkynes 2[a]
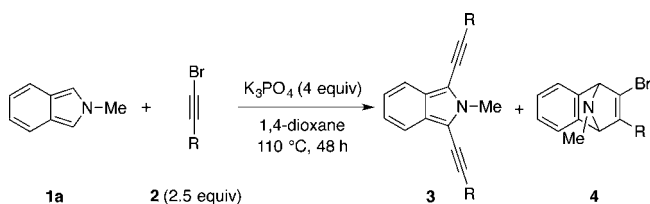
| entry	1-bromo-1-alkyne	yield of 3 (%)[b]	yield of 4 (%)[b]
1[c]	2a [R = Si(*i*-Pr)$_3$]	20 (3aa)	0 (4a)
2	2a	85 (3aa)	0 (4a)
3	2b [R = SiMe$_2$(*t*-Bu)]	84 (3b)	0 (4b)
4	2c (R = Ph)	0 (3c)	56 (4c)
5	2d (R = *n*-C$_6$H$_{13}$)	0 (3d)	76 (4d)
6	2e (R = *t*-Bu)	0 (3e)	81 (4e)

[a] 1a (0.20 mmol), 2 (0.50 mmol), and K$_3$PO$_4$ (0.80 mmol) were reacted in 1,4-dioxane (0.3 mL) at 110 °C for 48 h. [b] Isolated yield based on 1a. [c] In the absence of K$_3$PO$_4$.

The reaction of 1a with 2a was investigated in detail (eqs 1−3). When the reaction was carried out at lower temperature (60 °C), 4a was formed via [4 + 2] cycloaddi-tion (42%, eq 1). The isolated 4a was then heated at 110 °C in the presence of K$_3$PO$_4$ (eq 2), resulting in ring-opening of 4a with elimination of HBr to give 1-alkynylisoindole 5 in 73% yield. These results indicated that the C−H alky-nylation of isoindole proceeds through [4 + 2] cycloaddi-tion followed by ring-opening with elimination of HBr (Scheme 1).[14] The reaction also gave a small amount of 3aa (4%, eq 2), indicating that competitive retro-[4 + 2] cycloaddition gave 2a under these conditions (Scheme 1).[15] The isoindole 5 reacted with 2a at 110 °C in the presence of K$_3$PO$_4$ to give 3aa in 99% yield (eq 3). In the second alkynylation, the [4 + 2] cycloadduct was not observed, even in the reaction at lower temperature.
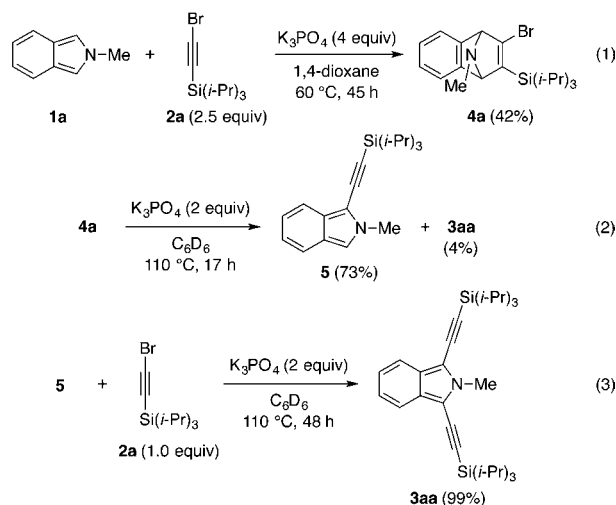
We then turned our attention to the synthesis of un-symmetrical 1,3-dialkynylisoindoles via alkynylation of monoalkynylated 5 (Table 2).[16] The reaction with 2b took place efficiently in 1,4-dioxane at 110 °C in the presence of

Scheme 1. Possible Mechanism of C−H Alkynylation
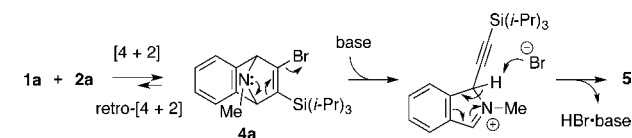
K$_3$PO$_4$ (2 equiv) to give 1,3-dialkynylisoindole **7a** bearing two different trialkylsilyl groups at the alkyne termini (entry 1). Note that the alkynylation of **5** also took place with phenyl- and *tert*-butyl-substituted **2c** and **2e**, which did not give the alkynylated products in the reaction with **1a** (entries 2 and 3). Unsymmetrical 1,3-dialkynylisoindoles **7d** and **7e** could also be synthesized via the reaction with 2-thienyl- and 3-pyridyl-substituted **2f** and **2g**, respectively (entries 4 and 5). These results indicate that **5** is a more suitable substrate than **1a** for the C−H alkynylation. 1,4-Bis(bromoethynyl)benzene (**2h**) reacted with 2 equiv of **5** to afford phenylene-linked **7f** in good yield (eq 4). These examples clearly demonstrate the utility of the cycloaddition-based alkynylation protocol for the synthesis of unsymmetrically substituted dialkynylated products.
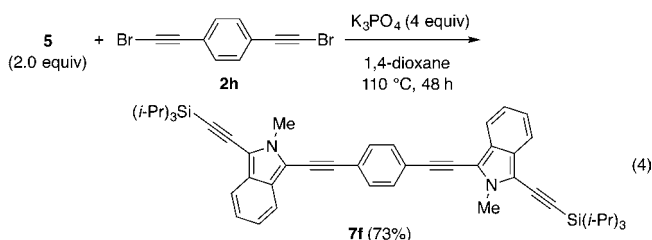
To enhance the synthetic utility of the C−H alkynylation, we then examined a one-pot synthesis of 1,3-dialkynylisoindoles from stable and easily available isoindolines **6** via palladium-catalyzed dehydrogenation (Table 3). As we established in previous studies,[7b] the corresponding isoindoles **1** were obtained in high yields via dehydrogenation of **6** in 1,4-dioxane at 110 °C in the presence of cyclohexene as a hydrogen acceptor and a catalytic amount of Pd(dba)$_2$ or Pd[P(*t*-Bu)$_3$]$_2$. However, one-pot C−H alkynylation of **2a** (2.5 equiv) in the presence of the dba- and P(*t*-Bu)$_3$-based palladium catalysts suffered from low yields under these conditions because of a side reaction of **2a** in the second

Table 2. C−H Alkynylation of **5** for the Synthesis of Unsymmetrical 1,3-Dialkynylisoindoles **7**[a]

entry	1-bromo-1-alkyne	temp (°C)/time (h)	yield (%)[b]
1	**2b** [R = SiMe$_2$(*t*-Bu)]	110/48	81 (**7a**)
2[c]	**2c** (R = Ph)	110/48	49 (**7b**)
3[c]	**2e** (R = *t*-Bu)	135/48	69 (**7c**)
4	**2f** (R = 2-thienyl)	110/24	60 (**7d**)
5	**2g** (R = 3-pyridyl)	110/24	79 (**7e**)

[a] **5** (0.15 mmol), **2** (0.18 mmol), and K$_3$PO$_4$ (0.30 mmol) were reacted in 1,4-dioxane (0.25 mL). [b] Isolated yield based on **5**. [c] **5** (0.20 mmol), **2** (0.24 mmol), and K$_3$PO$_4$ (0.40 mmol) in 1,4-dioxane (0.3 mL).

step.[17] We found that a dba- and P(*t*-Bu)$_3$-free palladium precursor, for example, Pd(OAc)$_2$, was suitable for this one-pot conversion (entries 1−9). In the C−H alkynylation step, isoindoles bearing *N*-Et, *N*-*i*-Pr, and *N*-*t*-Bu groups required prolonged reaction time or higher reaction temperature for high-yield formation of **3ab**, **3ac**, and **3ad** (entries 2−4). The C−H alkynylation was applicable to the isoindoles bearing methoxy, trifluoromethyl, or methyl groups in the six-membered ring (entries 5−7). It should be noted that sterically hindered 4,7-diphenylisoindole and 4,5,6,7-tetraphenylisoindole underwent C−H alkynylation to give **3ah** and **3ai** in high yields (entries 8 and 9). Along with **3aa**, **3ab**−**3ai** were stable under air and could be purified by column chromatography on silica gel.

The triisopropylsilyl group of **3aa** could be derivatized with retention of the isoindole structure (Scheme 2). Treatment of **3aa** with Bu$_4$NF in THF resulted in 1,3-diethynylisoindole **8** in 93% yield (left).[18] Desilylative Sonogashira coupling of **3aa** with aryl iodides afforded 1,3-di(arylethynyl)isoindoles **9a**−**9c** in high yields in the presence of AgF (right).[19]

Characteristic photophysical properties of the alkynylated isoindoles **3a**, **5**, **7**, and **9** are summarized in Table 4. The 1,3-bis(triisopropylsilylethynyl)isoindoles **3aa**−**3ai** showed two strong absorption maxima centered at 375−393 (λ_{ab1}) and 394−409 nm (λ_{ab2}). Some of these compounds showed two emission maxima centered at 407−422 (λ_{em1}) and 426−441 nm (λ_{em2}). As expected, red

(14) The ring-opening with elimination of HBr probably accelerated by β-effect of the silyl group. For β-effect of silyl group in elimination of sulfenic acid from β-silylvinyl sulfoxide, see: (a) Nakamura, S.; Kusuda, S.; Kawamura, K.; Toru, T. *J. Org. Chem.* **2002**, *67*, 640. For silicon-assisted elimination of HBr from β-silylvinyl bromide, see: (b) Jacobi, P. A.; Tassa, C. *Org. Lett.* **2003**, *5*, 4879.

(15) For examples of *retro*-[4 + 2] cycloaddition of isoindole adducts, see: (a) Bornstein, J.; Remy, D. E. *J. Chem. Soc. Chem. Commun.* **1972**, 1149. (b) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun.* **2006**, 661.

(16) A modified reaction conditions was established for preparation of **5**. **1a** was reacted with **2a** (1.0 equiv) in 1,4-dioxane at 110 °C in the presence of K$_3$PO$_4$ (2.0 equiv). After 2 h, heating was stopped. The reaction gave monoalkynylated **5** as a major product and it was isolated in 69% yield after distillation.

(17) Oxidative dimerization of **2a** took place to afford a significant amount of bis(triisopropylsilyl)butadiyne.

(18) Although **8** was able to handle in solution at low concentration, it was easily converted to black-colored, structure-undefined higher molecular weight compounds after concentration.

(19) For desilylative Sonogashira coupling, see: Nishihara, Y.; Inoue, E.; Noyori, S.; Ogawa, D.; Okada, Y.; Iwasaki, M.; Takagi, K. *Tetrahedron* **2012**, *68*, 4869 and references therein.

(20) For the effect of trimethylsilylethynyl group on the fluorescence quantum yield of pyrene, see: Maeda, H.; Maeda, T.; Mizuno, K.; Fujimoto, K.; Shimizu, M.; Inoue, M. *Chem.—Eur. J.* **2006**, *12*, 824.

Table 3. One-pot Synthesis of 1,3-Dialkynylisoindoles **3a** from Isoindolines **6**[a]
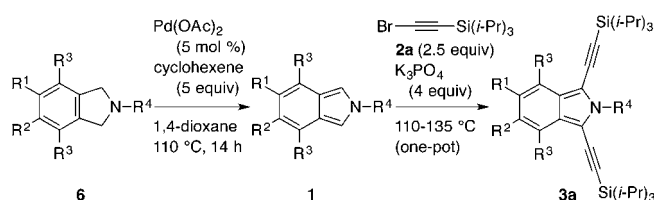
entry	R^1	R^2	R^3	R^4		temp (°C)/time (h) in the second step	yield of **3a** (%)[b]
1[c]	H	H	H	Me	**6a**	110/48	71 (**3aa**)
2	H	H	H	Et	**6b**	110/72	83 (**3ab**)
3	H	H	H	i-Pr	**6c**	135/48	88 (**3ac**)
4	H	H	H	t-Bu	**6d**	135/48	90 (**3ad**)
5	OMe	H	H	Me	**6e**	135/24	67 (**3ae**)
6	CF$_3$	H	H	Me	**6f**	135/24	88 (**3af**)
7	Me	Me	H	Me	**6g**	135/48	55 (**3ag**)
8[d]	H	H	Ph	Me	**6h**	135/72	79 (**3ah**)
9[d]	Ph	Ph	Ph	Me	**6i**	135/24	86 (**3ai**)

[a] Pd(OAc)$_2$ (0.015 mmol), cyclohexene (1.5 mmol), and **6** (0.30 mmol) were reacted in 1,4-dioxane (0.45 mL) at 110 °C for 14 h. **2a** (0.75 mmol) and K$_3$PO$_4$ (1.2 mmol) were then added to the mixture and the resulting mixture was stirred at 110−135 °C for 24−72 h. [b] Isolated yield based on **6**. [c] 0.4 mmol scale reaction. [d] 0.2 mmol scale reaction.

Scheme 2. Desilylative Conversion of **3aa**
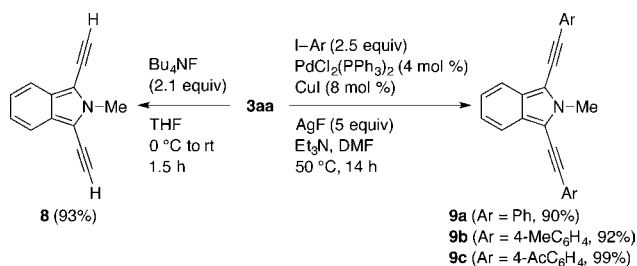
shifts of both absorption maxima (449 and 476 nm) and emission maxima (493 and 533 nm) were observed in the spectra of phenylene-linked **7f**. Strong fluorescence was observed for **3aa-3ag**, **7a**, and **7c** (Φ 0.83−0.92),[20] whereas **7b**, **7d**, and **7e**, which bear an arylethynyl group, showed very weak fluorescence (Φ 0.001−0.01).

In conclusion, we have established an efficient method for synthesis of both symmetrical and unsymmetrical

Table 4. Photophysical Properties of Alkynylated Isoindoles **3a**, **5**, **7**, and **9** in CH$_2$Cl$_2$

	absorption		emission[a]		
	λ_{max}/nm (log ε)		λ_{max}/nm		
isoindole	λ_{ab1}	λ_{ab2}	λ_{em1}	λ_{em2}	Φ[b]
3aa	376 (4.53)	396 (4.60)	407	426	0.88
3ab	375 (4.43)	395 (4.50)	407	427	0.86
3ac	377 (4.48)	396 (4.55)	410	429	0.89
3ad	382 (4.48)	402 (4.54)	418	435	0.83
3ae	374 (4.42)	394 (4.49)	422	441	0.90
3af	382 (4.33)	400 (4.36)	431		0.92
3ag	375 (4.50)	394 (4.56)	407	426	0.90
3ah	393 (4.35)	409 (4.39)	461		0.20
3ai	389 (4.35)	409 (4.39)	449		0.72
5[c]	353 (4.41)		406		0.57
7a	375 (4.50)	395 (4.57)	406	426	0.86
7b	395 (4.59)	416 (4.66)	450		0.01
7c	374 (4.37)	392 (4.40)	411	427	0.84
7d	401 (4.46)	424 (4.43)	457	486	0.001
7e	397 (4.53)	419 (4.65)	453	486	0.01
7f	449 (4.85)	476 (4.89)	493	533	0.66
9a	414 (4.62)	434 (4.57)	445	472	0.13
9b	413 (4.72)	434 (4.71)	446	474	0.23
9c[c]	475 (4.81)		528		0.03

[a] Excited at the wavelength of λ_{ab2}. [b] Absolute PL quantum yield. [c] Emission was excited at the wavelength of λ_{ab1}.

1,3-dialkynylisoindoles via C−H alkynylation of isoindoles. The reaction proceeded via [4 + 2] cycloaddition followed by a ring-opening reaction. Remarkable stability under air and strong fluorescence were observed for some alkynylated isoindoles. The synthetic methodology and the fundamental insights into chemical and physical properties shown here would be valuable in development of new functional molecules based on alkynylisoindoles.

Supporting Information Available. Experimental details and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.