ORGANIC LETTERS

2009
Vol. 11, No. 11
2269−2272

Three-Component Synthesis of *N*-Boc-4-iodopyrroles and Sequential One-Pot Alkynylation[||]

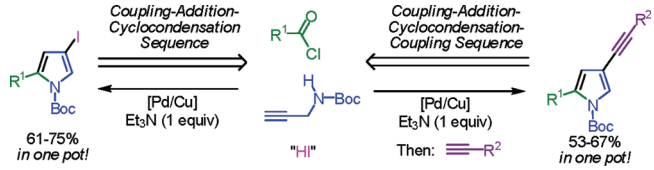
Eugen Merkul,[†] Christina Boersch,[†] Walter Frank,[‡,§] and Thomas J. J. Müller*[,†]

Institut für Organische Chemie und Makromolekulare Chemie and Institut für Anorganische Chemie und Strukturchemie, Heinrich-Heine-Universität Düsseldorf, Universitätsstrasse 1, D-40225 Düsseldorf, Germany

thomasjj.mueller@uni-duesseldorf.de

Received March 19, 2009

ABSTRACT



(Hetero)aryl-, alkenyl-, and selected alkyl-substituted acid chlorides can be efficiently coupled with *N*-Boc-protected propargylamine to produce ynones which are converted in a one-pot fashion to 2-substituted *N*-Boc-4-iodopyrroles. Upon addition of a further alkyne, another Sonogashira coupling can be carried out in a one-pot fashion. This sequentially Pd/Cu-catalyzed process represents a very mild and efficient entry to 2,4-disubstituted *N*-Boc-pyrroles.

Among five-membered heterocycles, pyrroles are the most prominent ones[1] since they constitute important classes of natural products,[2] synthetic pharmaceuticals,[3] and electrically conducting materials such as polypyrroles.[4] Therefore, the development of new pyrrole syntheses and synthetic strategies has remained an ongoing challenge.[5] In particular, multicomponent approaches have inevitably become increasingly important due to their elegance and practicability.[6] Furthermore, the quest for mild synthetic methods for compounds with unusual substitution patterns such as 2,4-disubstituted pyrroles has turned out to be nontrivial.[7] As part of our program to develop multicomponent syntheses of heterocycles initiated by transition-metal catalysis,[8] a strategy based upon alkynones via Sonogashira coupling[9] becomes apparent. Here, we communicate a concise, one-pot synthesis of Boc-protected 2-substituted 4-iodopyrroles and first examples of sequentially Pd/Cu-catalyzed subsequent alkynylations, also in a one-pot fashion.

In the past years, the Sonogashira coupling of acid chlorides with terminal alkynes using only 1 equiv of triethylamine has proven to be a very effective tool for the formation of ynones,[10] which can be further reacted with various nucleophiles in a one-pot fashion,[11] opening an entry to many consecutive multicomponent syntheses of hetero-

[||] Dedicated to Prof. Dr. Matthias W. Haenel on the occasion of his 65th birthday.

[†] Institut für Organische Chemie and Makromolekulare Chemie.

[‡] Institut für Anorganische Chemie and Strukturchemie.

[§] X-ray structure analysis.

(1) For some recent reviews, see: (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264. (b) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095. (c) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (d) Banwell, M. G.; Goodwin, T. E.; Ng, S.; Smith, J. A.; Wong, D. J. *Eur. J. Org. Chem.* **2006**, 3043. (e) Fürstner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 3582. (f) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753.

(2) For excellent reviews, see, e.g.: (a) Gossauer, A. *Die Chemie der Pyrrole*; Springer Verlag: Berlin, 1974. (b) Gossauer, A. In *Houben-Weyl, Methoden der Organischen Chemie*; Kreher, R., Ed.; G. Thieme Verlag: Stuttgart, 1994; Bd. E6a, p 556. (c) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 119. (d) Fürstner, A. *Synlett* **1999**, 1523.

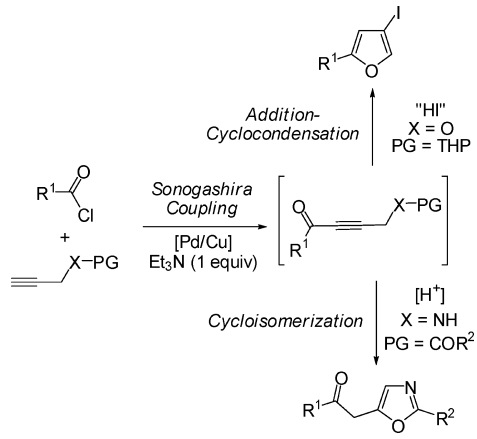
(3) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, 1996; Vol. 2, p 207.

(4) For an interesting review, see, e.g.: MacDiarmid, A. G. *Synth. Met.* **1997**, *84*, 27.

10.1021/ol900581a CCC: $40.75
Published on Web 05/08/2009

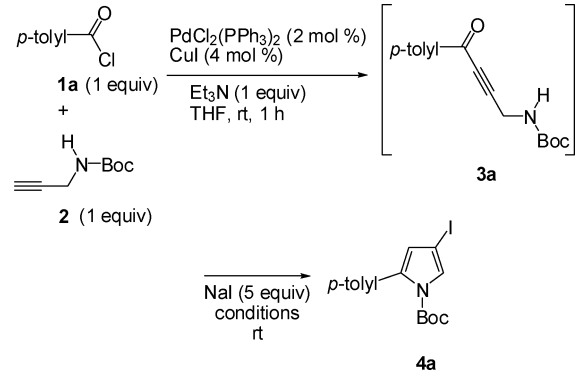
cycles.[8,9] Most interestingly, the subsequent additions to alkynones are restricted to not only Brønsted basic conditions but also Brønsted acid mediated transformations for the one-pot synthesis of halofurans,[12] and oxazoles[13] via the intermediacy of propargyl ketone derivatives can be easily realized as a consequence of the mild reaction conditions of the Sonogashira coupling (Scheme 1).

Scheme 1. Switching Conditions from Brønsted Basic to Brønsted Acidic Conditions Leading to Coupling−Addition−Cyclocondensation and Coupling−Cycloisomerization Sequences via Propargyl Ketone Derivatives



Halopyrroles[14,15] are valuable synthetic building blocks for synthetic transformations, and therefore, a multicomponent access would be highly desirable. For the three-component synthesis of the 4-iodopyrroles with a nitrogen protecting group, propargyl amides appear to be the most suitable starting materials. Since the cycloisomerization to an oxazole under acidic conditions could jeopardize this endeavor, the choice of the right nitrogen protecting group plays a key role. The Boc group is a versatile carbamate protecting group for the pyrrole nitrogen atom, useful for many transformations on the pyrrole core and easily removable. Therefore, upon reacting toluoyl chloride (**1a**) and *N*-Boc-protected propargylamine (**2**) under modified Sonogashira conditions, the intermediate alkynone **3a**[16] was obtained. Without isolation, the concluding addition−cyclocondensation furnishes the *N*-Boc-4-iodo-2-*p*-tolylpyrrole (**4a**) (Scheme 2). The final addition−cyclocondensation step

Scheme 2. Optimization of the One-Pot Coupling−Addition−Cyclocondensation Synthesis of 4-Iodopyrrole **4a**



was optimized for the sequence by variation of the amount of PTSA · H_2O, the added cosolvent, and the reaction time

(5) For some recent syntheses, see: (a) Kim, Y.; Kim, J.; Park, S. B. *Org. Lett.* **2009**, *11*, 17. (b) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem.—Eur. J.* **2009**, *15*, 227. (c) Wang, Y.-F.; Toh, K. K.; Chiba, S.; Narasaka, K. *Org. Lett.* **2008**, *10*, 5019. (d) Cacchi, S.; Fabrizi, G.; Filisti, E. *Org. Lett.* **2008**, *10*, 2629. (e) Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Moscatelli, G.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983. (f) Chiba, S.; Wang, Y.-F.; Lapointe, G.; Narasaka, K. *Org. Lett.* **2008**, *10*, 313. (g) Zhang, Z.; Zhang, J.; Tan, J.; Wang, Z. *J. Org. Chem.* **2008**, *73*, 5180. (h) Yin, G.; Wang, Z.; Chen, A.; Gao, M.; Wu, A.; Pan, Y. *J. Org. Chem.* **2008**, *73*, 3377. (i) Bremner, W. S.; Organ, M. G. *J. Comb. Chem.* **2008**, *10*, 142. (j) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. *Org. Lett.* **2007**, *9*, 5191. (k) Martín, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379. (l) Istrate, F. M.; Gagosz, F. *Org. Lett.* **2007**, *9*, 3181. (m) Shindo, M.; Yoshimura, Y.; Hayashi, M.; Soejima, H.; Yoshikawa, T.; Matsumoto, K.; Shishido, K. *Org. Lett.* **2007**, *9*, 1963. (n) Reeves, J. T.; Song, J. J.; Tan, Z.; Lee, H.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2007**, *9*, 1875. (o) Peng, L.; Zhang, X.; Ma, J.; Zhong, Z.; Wang, J. *Org. Lett.* **2007**, *9*, 1445. (p) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973. (q) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744. (r) Milgram, B. C.; Eskildsen, K.; Richter, S. M.; Scheidt, W. R.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 3941. (s) Misra, N. C.; Panda, K.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2007**, *72*, 1246. (t) Shi, D.; Dou, G.; Shi, C.; Li, Z.; Ji, S.-J. *Synthesis* **2007**, 3117. (u) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, *8*, 5837. (v) Winkler, J. D.; Ragains, J. R. *Org. Lett.* **2006**, *8*, 4031. (w) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (x) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835. (y) Nad, S.; Roller, S.; Haag, R.; Breinbauer, R. *Org. Lett.* **2006**, *8*, 403. (z) Martín, R.; Rodríguez Rivero, M.; Buchwald, S. L. *Angew. Chem. Int. Ed* **2006**, *45*, 7079. (aa) Freifeld, I.; Shojaei, H.; Langer, P. *J. Org. Chem.* **2006**, *71*, 4965. (bb) Fuchibe, K.; Ono, D.; Akiyama, T. *Chem. Commun.* **2006**, 2271. (cc) Peschko, C.; Winklhofer, C.; Terpin, A.; Steglich, W. *Synthesis* **2006**, 3048. (dd) Spaggiari, A.; Vaccari, D.; Davoli, P.; Prati, F. *Synthesis* **2006**, 995. (ee) Magnus, N. A.; Staszak, M. A.; Udodong, U. E.; Wepsiec, J. P. *Org. Process Res. Dev.* **2006**, *10*, 899. (ff) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313. (gg) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (hh) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (ii) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (jj) Bharadwaj, A. R.; Scheidt, K. A. *Org. Lett.* **2004**, *6*, 2465. (kk) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389. (ll) Siriwardana, A. I.; Kathriarachchi, K. K. A. D. S.; Nakamura, I.; Gridnev, I. D.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 13898. (mm) Yu, M.; Pagenkopf, B. L. *Org. Lett.* **2003**, *5*, 5099. (nn) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853. (oo) Bullington, J. L.; Wolff, R. R.; Jackson, P. F. *J. Org. Chem.* **2002**, *67*, 9439. (pp) Smith, N. D.; Huang, D.; Cosford, N. D. P. *Org. Lett.* **2002**, *4*, 3537. (qq) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (rr) Grigg, R.; Savic, V. *Chem. Commun.* **2000**, 873.

(6) For a recent highlight describing multicomponent strategies, see: Balme, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 6238. For some recent multicomponent pyrrole syntheses, see: (a) Lu, Y.; Arndtsen, B. A. *Org. Lett.* **2009**, *11*, 1369. (b) Tejedor, D.; López-Tosco, S.; González-Platas, J.; García-Tellado, F. *Chem.—Eur. J.* **2009**, *15*, 838. (c) Yadav, J. S.; Reddy, B. V. S.; Srinivas, M.; Divyavani, C.; Basha, J.; Sarma, A. V. S. *J. Org. Chem.* **2008**, *73*, 3252. (d) Lu, Y.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 5430. (e) Khalili, B.; Jajarmi, P.; Eftekhari-Sis, B.; Hashemi, M. M. *J. Org. Chem.* **2008**, *73*, 2090. (f) Liu, X.-t.; Huang, L.; Zheng, F.-j.; Zhan, Z.-p. *Adv. Synth. Catal.* **2008**, *350*, 2778. (g) Galliford, C. V.; Scheidt, K. A. *J. Org. Chem.* **2007**, *72*, 1811. (h) Cyr, D. J. S.; Martin, N.; Arndtsen, B. A. *Org. Lett.* **2007**, *9*, 449. (i) Cyr, D. J. S.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2007**, *129*, 12366. (j) Cadierno, V.; Gimeno, J.; Nebra, N. *Chem.—Eur. J.* **2007**, *13*, 9973. (k) Tejedor, D.; González-Cruz, D.; García-Tellado, F.; Marrero-Tellado, J. J.; Rodríguez, M. L. *J. Am. Chem. Soc.* **2004**, *126*, 8390. (l) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468. (m) Braun, R. U.; Müller, T. J. J. *Synthesis* **2004**, 2391. (n) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681. (o) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297.

Table 1. Optimization of the Final Addition−Cyclocondensation Step within the One-Pot Three-Component Synthesis of 4-Iodopyrrole **4a**

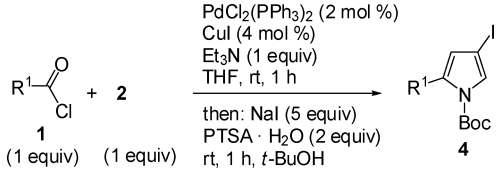
entry	PTSA · H_2O (equiv)	added cosolvent	reaction time (h)	4-iodopyrrole **4a** (isolated yield, %)
1	1.0	MeOH	22[a]	60
2	1.0	*t*-BuOH	19[a]	65
3	2.0	*t*-BuOH	19	70
4	2.0	*t*-BuOH	1	69

[a] After 1 h the reaction was not complete according to TLC monitoring.

(Table 1). The best conditions smoothly provided the desired product **4a** in 69% isolated yield within 1 h upon applying 2 equiv of PTSA·H_2O and *t*-BuOH as the alcoholic additive (entry 4). Interestingly, the yields of **4a** were higher than that of the isolated intermediate ynone **3a**.[16]

With this mild, quick and practical protocol in hand we set out to screen the scope of this reaction (Scheme 3, Table

Scheme 3. One-Pot Three-Component Synthesis of 4-Iodopyrroles **4**



2). Upon upscaling to a 5 mmol level, an even higher yield of the 4-iodopyrrole **4a** can be obtained (Table 2, entry 1 vs Table 1, entry 4). Further upscaling to 30 mmol furnished compound **4d** in 77% isolated yield (73% yield on the 5 mmol scale, Table 2, entry 4). The structures of the 4-iodopyrroles **4** were unambiguously assigned by spectroscopic characterization and combustion analysis and later corroborated by an X-ray crystal structure analysis for compound **4d** (Figure 1).[17]

The sequence starts with easily accessible starting materials and gives good yields of 4-iodopyrroles **4**, and it is easy to perform with a simple catalyst system and under mild conditions.[18] It was found to be quite general with respect to the underlying acid chlorides **1**. Aromatic substituents bearing electroneutral (entry 5), electron-withdrawing (entries 6 and 7), and electron-donating (entries 1−4) substituents even in the *ortho*-position (entry 3) are tolerated. Furthermore, heteroaryl (entry 8), alkenyl (entry 9), cyclopropyl (entry 10), and sterically demanding adamantyl (entry 11) substituents can be effectively carried through the sequence.

Table 2. One-Pot Three-Component Synthesis of 4-Iodopyrroles **4**

entry	acid chloride **1**	4-iodo pyrrole **4** (isolated yield %)[a]
1	R^1 = *p*-MeC_6H_4 (**1a**)	*p*-tolyl, **4a** (73%)
2	R^1 = *m*-MeC_6H_4 (**1b**)	*m*-tolyl, **4b** (74%)
3	R^1 = *o*-MeC_6H_4 (**1c**)	*o*-tolyl, **4c** (72%)
4	R^1 = *p*-$MeOC_6H_4$ (**1d**)	*p*-$MeOC_6H_4$, **4d** (73%)
5	R^1 = Ph (**1e**)	Ph, **4e** (72%)
6	R^1 = *p*-ClC_6H_4 (**1f**)	*p*-ClC_6H_4, **4f** (62%)
7	R^1 = *p*-FC_6H_4 (**1g**)	*p*-FC_6H_4, **4g** (75%)
8	R^1 = 2-thienyl (**1h**)	2-thienyl, **4h** (63%)
9	R^1 = β-styryl (**1i**)	β-styryl, **4i** (70%)[b]
10	R^1 = cyclopropyl (**1j**)	cyclopropyl, **4j** (69%)[c]
11	R^1 = 1-adamantyl (**1k**)	1-adamantyl, **4k** (61%)[b]

[a] All reactions were performed on 5 mmol scale. [b] The reaction time for the coupling step was 21 h. [c] The reaction time for the coupling step was 3 h.

However, for nonaromatic acid chlorides, the reaction times of coupling were slightly longer than 1 h.

(7) (a) Kiren, S.; Hong, X.; Leverett, C. A.; Padwa, A. *Org. Lett.* **2009**, *11*, 1233. (b) Zanatta, N.; Schneider, J. M. F. M.; Schneider, P. H.; Wouters, A. D.; Bonacorso, H. G.; Martins, M. A. P.; Wessjohann, L. A. *J. Org. Chem.* **2006**, *71*, 6996. (c) Rosenmund, P.; Grübel, K. *Angew. Chem.* **1968**, *80*, 702.

(8) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.

(9) (a) Willy, B.; Müller, T. J. J. *ARKIVOC* **2008**, *1*, 195. (b) Müller, T. J. J. *Chim. Oggi/Chem. Today* **2007**, *25*, 70. (c) Müller, T. J. J. *Targets Heterocycl. Systems* **2006**, *10*, 54.

(10) (a) Karpov, A. S.; Müller, T. J. J. *Org. Lett.* **2003**, *5*, 3451. (b) D'Souza, D. M.; Müller, T. J. J. *Nat. Protoc.* **2008**, *3*, 1660.

(11) (a) Karpov, A. S.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2004**, 1502. (b) Karpov, A. S.; Müller, T. J. J. *Synthesis* **2003**, 2815.

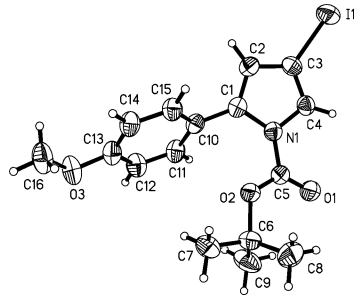
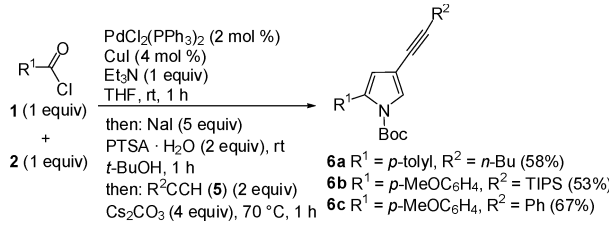


Figure 1. ORTEP plot of compound **4d**.

The obtained 4-iodopyrroles **4** are highly useful synthetic building blocks,[19] and the first scouting experiments were performed in the sense of a sequentially Pd/Cu-catalyzed reaction[20] since the catalyst system should be still operative after the coupling−addition−cyclocondensation sequence. Therefore, just upon addition of another terminal alkyne **5** to the reaction mixture, *N*-Boc-2-aryl-4-alkynylpyrroles **6** were obtained in good yields (Scheme 4). The conditions are sufficiently mild to leave the Boc group uncleaved. In comparison to the coupling−addition−cyclocondensation−coupling one-pot synthesis (58% yield), the two-step synthesis of the alkynyl pyrrole **6a** furnishes a comparable overall yield (61%).

Scheme 4. Coupling−Addition−Cyclocondensation−Coupling Sequence to 4-Alkynyl-*N*-Boc-pyrroles **6**



In conclusion, we disclose an efficient one-pot three-component synthesis of 2-substituted *N*-Boc-4-iodopyrroles that can easily be upscaled to multigrams, and we also show preliminary examples of a coupling−addition−cyclocondensation−coupling sequence to 4-alkynyl-*N*-Boc-pyrroles in good yields. This latter principle appears to be quite general and further terminating cross-coupling reactions can be easily envisioned. Studies taking advantage of this versatile one-pot multicomponent strategy to iodopyrroles as valuable building blocks for the synthesis of 2,4-disubstituted pyrrole derivatives are currently underway.

Acknowledgment. The financial support of this work by Merck Serono, Darmstadt, and the Fonds der Chemischen Industrie is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of compounds **3a**, **3b**, **4**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Eur. J. Org. Chem.* **2006**, 2991. (b) Karpov, A. S.; Merkul, E.; Oeser, T.; Müller, T. J. J. *Chem. Commun.* **2005**, 2581.

(13) (a) Merkul, E.; Grotkopp, O.; Müller, T. J. J. *Synthesis* **2009**, 502. (b) Merkul, E.; Müller, T. J. J. *Chem. Commun.* **2006**, 4817.

(14) For noncatalytic accesses to halopyrroles from ynones, see: (a) Ghosez, L.; Franc, C.; Denonne, F.; Cuisinier, C.; Touillaux, R. *Can. J. Chem.* **2001**, *79*, 1827. (b) Franc, C.; Denonne, F.; Cuisinier, C.; Ghosez, L. *Tetrahedron Lett.* **1999**, *40*, 4555. (c) Masquelin, T.; Obrecht, D. *Synthesis* **1995**, 276.

(15) For coupling reactions with iodopyrroles, see: Liu, J.-H.; Chan, H.-W.; Wong, H. N. C. *J. Org. Chem.* **2000**, *65*, 3274.

(16) The alkynone **3a** can be isolated and was obtained in 59% yield.

(17) Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 723307 (**4d**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk).

(18) **Typical procedure (4d).** $PdCl_2(PPh_3)_2$ (70 mg, 0.10 mmol) and CuI (39 mg, 0.20 mmol) were placed under argon in a flame-dried screw-cap vessel. Then 25 mL of dry THF was added, and the mixture was degassed with argon. Dry triethylamine (0.69 mL, 5.00 mmol), 4-methoxybenzoyl chloride (**1d**) (879 mg, 5.00 mmol), and *tert*-butyl prop-2-ynylcarbamate (**2**) (776 mg, 5.00 mmol) were successively added to the mixture which was then stirred at room temperature for 1 h. Then, sodium iodide (3.79 g, 25.0 mmol), toluene-4-sulfonic acid monohydrate (1.94 g, 10.0 mmol), and 5 mL of *tert*-butyl alcohol were successively added to the mixture, which was stirred at room temperature for 1 h. The reaction mixture was diluted with 50 mL of brine, the phases were separated, and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried with anhydrous sodium sulfate. After removal of the solvents in vacuo, the residue was absorbed onto Celite and chromatographed on silica gel with petroleum ether (boiling range 40−60 °C)/ethyl acetate (PE−EE = 100:1) to give 1.46 g (73%) of analytically pure *tert*-butyl 4-iodo-2-(4-methoxyphenyl)-1*H*-pyrrole-1-carboxylate (**4d**) as a colorless solid: mp 71−72 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.39 (s, 9 H), 3.82 (s, 3 H), 6.20 (d, J = 1.9 Hz, 1 H), 6.88 (d, J = 8.8 Hz, 2 H), 7.24 (d, J = 8.8 Hz, 2 H), 7.39 (d, J = 1.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.6 (CH_3), 55.3 (CH_3), 64.4 (C_{quat}), 84.2 (C_{quat}), 113.1 (CH), 120.3 (CH), 125.3 (C_{quat}), 126.7 (CH), 130.4 (CH), 136.5 (C_{quat}), 147.9 (C_{quat}), 159.3 (C_{quat}); EI + MS (/z) 399 (M^+, 3), 343 ($(M - C_4H_8)^+$, 11), 299 ($(M - C_5H_8O_2)^+$, 16), 298 ($(M - C_5H_9O_2)^+$, 13), 171 ($(M - C_5H_9O_2I)^+$, 6), 156 (12), 128 (11), 57 ($C_4H_9^+$, 100), 41 (34); IR (KBr) $\tilde{\nu}$ 1734 cm^{-1}, 1511, 1370, 1337, 1293, 1251, 1180, 1151, 1032, 847, 808. Anal. Calcd for $C_{16}H_{18}INO_3$ (399.2): C, 48.14; H, 4.54; N, 3.51. Found: C, 48.36; H, 4.37; N, 3.34.

(19) Boc as an electron-withdrawing group allows the 4-iodopyrroles **4**, which are notoriously unstable with electron-donating groups at the pyrrole nitrogen, to be handled. They are storable for months in refrigerator under argon without decomposition.

(20) (a) For a review, see e.g.: Müller, T. J. J. *Top. Organomet. Chem.* **2006**, *19*, 149. (b) For recent examples, see e.g.: Liao, W.-W.; Müller, T. J. J. *Synlett* **2006**, 3469. (c) See also ref 12b.