JOC*Article*

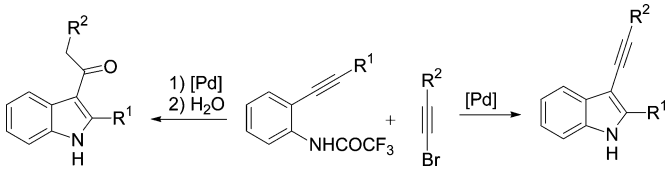
Palladium-Catalyzed Reaction of *o*-Alkynyltrifluoroacetanilides with 1-Bromoalkynes. An Approach to 2-Substituted 3-Alkynylindoles and 2-Substituted 3-Acylindoles

Antonio Arcadi,[†] Sandro Cacchi,*[,‡] Giancarlo Fabrizi,[‡] Fabio Marinelli,[†] and Luca M. Parisi[‡]

Dipartimento di Chimica Ingegneria Chimica e Materiali della Facoltà di Scienze, Università di L'Aquila, Via Vetoio, Coppito Due, I-67100 L'Aquila, Italy, and Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università degli Studi "La Sapienza", P. le A. Moro 5, 00185 Rome, Italy

sandro.cacchi@uniroma1.it

Received March 15, 2005

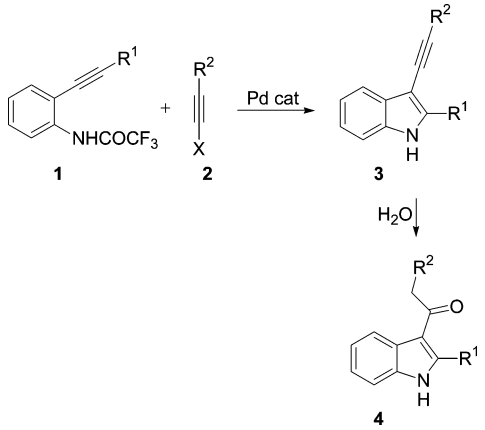


The palladium-catalyzed reaction of *o*-alkynyltrifluoroacetanilides with 1-bromoalkynes affords free N−H 2-substituted 3-alkynylindoles in satisfactory to high yield. 2-Substituted 3-alkynylindoles revealed useful intermediates for the regioselective synthesis of 2-substituted 3-acylindoles. The latter can be prepared from *o*-alkynyltrifluoroacetanilides and 1-bromoalkynes via a one-pot cyclization−hydration protocol, omitting the isolation of 2-substituted 3-alkynylindoles.

Introduction

The construction of the functionalized pyrrole ring incorporated into the indole system through our aminopalladation−reductive elimination reaction has been shown to be a simple and versatile tool for a rapid assembly of indole derivatives with a high level of molecular complexity from acyclic precursors.[1] The reaction tolerates a wide range of functional groups amenable to further functionalization, so that even higher structural complexity can be readily achieved.[2] In connection with our current research interests in this area and in order to widen the scope and generality of the methodology, we decided to develop a procedure for the preparation of 2-substituted 3-alkynylindoles through the palladium-catalyzed reaction of readily available *o*-alkynyltrifluoroacetanilides with 1-haloalkynes (Scheme 1).

SCHEME 1



1-Halo-1-alkynes have never been used in this indole chemistry. In general, they have been rarely used in the functionalization of alkynes through reactions involving intramolecular nucleophilic attack across the carbon−carbon triple bond activated by coordination to an organopalladium complex.[3] To the best of our knowledge, only a couple of examples of this type of reaction have been reported. One of them is due to Balme et al. who first described the utilization of 1-halo-1-alkynes in the synthesis of 5-(*E*)-alkylidene tetrahydro-2-furanones from

[†] Università di L'Aquila.
[‡] Università degli Studi "La Sapienza".

(1) For a review, see: (a) Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Eur. J. Org. Chem.* **2002**, 2671. See also: (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Synthesis* **2004**, 1889. (c) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Tetrahedron Lett.* **2004**, *45*, 2431 (d) Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. *Synthesis* **2003**, 728. (e) Flynn, B. L.; Hamel, E.; Jung, M. K. *J. Med. Chem.* **2002**, *45*, 2670.

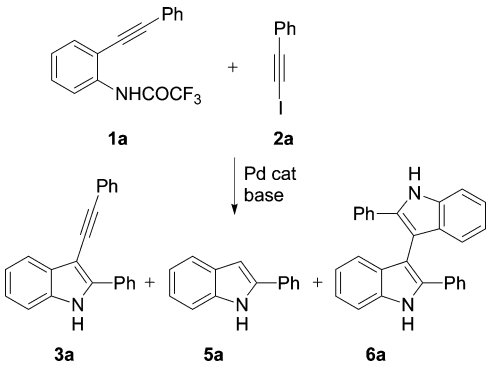
(2) (a) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (b) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437.

10.1021/jo050517z CCC: $30.25
Published on Web 07/07/2005

pentynoic acids.[4] The other one was recently reported by Larock and co-workers, who described the preparation of 3,4-disubstituted isoquinolines via intramolecular cyclization of *N-tert*-butyl-*o*-(1-alkynyl)benzaldimines promoted by a variety of organopalladium complexes, including *σ*-alkynylpalladium complexes.[5] On the other hand, some indole derivatives containing 3-alkynyl substituents have been shown to exhibit interesting biological activities.[6] Furthermore, the introduction of the alkyne functionalilty into the indole system appears particularly suited for further elaboration of indoles. For example, alkynylindoles have been reported to be useful intermediates for the synthesis of carbolines.[7] Particularly, in connection with our interest in the synthesis of 3-acylindoles,[1b,2,8] we envisaged that 3-alkynylindoles could be useful precursors of this important class of indole derivatives[9,10] through the regioselective[11,12] addition of water.

Hereafter we wish to report the results of this study.

SCHEME 2



Results and Discussion

Initial attempts focused on exploring the feasibility of the transformation. *o*-(Phenylethynyl)trifluoroacetanilide **1a** and 1-iodo-phenylacetylene **2a** were used as the model system (Scheme 2), and the following reaction variables were examined: the nature of the phosphine ligand, the base, the solvent, and the reaction temperature. All reactions were conducted on a 0.35 mmol scale in 2 mL of solvent under argon, using 1.2 equiv of **2a**, 5 mol % of palladium, 10 mol % of phosphine ligand, and 3 equiv of base. Compound **1a** was prepared from *o*-iodoaniline via Sonogashira coupling with phenylacetylene, followed by the reaction of the resulting coupling product with trifluoroacetic anhydride according to the previously described procedure.[13] 1-Iodophenylacetylene was prepared from the reaction of phenylacetylene with ethylmagnesium bromide followed by treatment with iodine.[14] Some results from that study are summarized in Table 1.

Under a variety of reaction conditions, the desired indole derivative **3a** was isolated in low yields, the main reaction product being 2-phenylindole **5a** (Table 1, entries 2−4) or the biindole **6a** (Table 1, entries 5−7). Apparently, in analogy to previous findings,[4] 1-iodophenylacetylene is not a good partner for aminopalladation-reductive elimination reactions, most probably because of its tendency to undergo side reactions we have not investigated (for example, 1-iodoalkynes have been recently shown to undergo palladium-catalyzed homocoupling to give 1,3-diynes).[15]

We have since explored the utilization of 1-bromophenylacetylene **2b**, prepared by reaction of phenylacetylene with silver nitrate and *N*-bromosuccinimide,[16] and have found that the reaction of **2b** with **1a** in the presence of $Pd(PPh_3)_4$ as the palladium(0) source and K_2CO_3 as the base, in DMSO, DMF, or MeCN at 60 °C affords the corresponding 3-alkynyl derivative in good yields (Table 1, entries 8−10) with a higher reaction rate in DMF. Similar yield and reaction rate as high as in DMF was observed with Cs_2CO_3 in MeCN (Table 1, compare entry 9 with entry 11). The use of $Pd(OAc)_2$ and PPh_3 was also

(3) For recent reviews on this type of chemistry, see the following. Cyclization with nitrogen nucleophiles: (a) Cacchi, S.; Marinelli, F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 2, p 2227. (b) Cacchi, S.; Fabrizi, G.; Parisi, L. M. *Heterocycles* **2002**, *58*, 667. Cyclization with oxygen nucleophiles: (c) Cacchi, S.; Arcadi, A. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 2, p 2193. (d) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Heterocycles* **2002**, *56*, 613. Cyclization with carbon nucleophiles: (e) Balme, G.; Bouyssi, D.; Monteiro, N. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 2, p 2245. See also: (f) Balme, G. Bossharth, E. Monteiro, N. *Eur. J. Org. Chem.* **2003**, 4101. (g) Balme, G.; Bouyssi, D.; Lomberget, T. Monteiro, N. *Synthesis* **2003**, 2115.

(4) Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron Lett.* **1992**, *33*, 2811.

(5) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920.

(6) (a) Hewkin, C. T.; Fabio, R.; Conti, N.; Cugola, A.; Gastaldi, P.; Micheli, F.; Quaglia, A. M. *Arch. Pharm. Pharm. Med. Chem.* **1999**, *332*, 55. (b) Cugola, A.; Gaviraghi, G.; Micheli, F. Patent WO 9420465, 1994; *Chem. Abstr.* **1994**, *121*, 300763.

(7) (a) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048. (b) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793. (c) Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, 2477.

(8) Battistuzzi, G.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *Org. Lett.* **2002**, *4*, 1355.

(9) For some recent utilizations of 3-acylindoles as intermediates, see: (a) Hendrickson, J. B.; Wang, *J. Org. Lett.* **2004**, *6*, 3. (b) Na, Y.-M.; Le Borgne, M.; Pagniez, F.; Le Baut, G.; Le Pape, P. *Eur. J. Med. Chem.* **2003**, 75. (c) Fresneda, P. M.; Molina, P.; Delgado, S.; Bleda, J. A. *Tetrahedron Lett.* **2000**, *41*, 4777. (d) Fresneda, P. M.; Molina, P.; Saez, M. A. *Synlett* **1999**, 1651. (e) Faul, M. M.; Winneroski, L. L.; Krumrich, C. A. *J. Org. Chem.* **1998**, *63*, 6053. (f) Wang, S.-P. *Heterocycles* **1997**, *45*, 347.

(10) For some references on biological activities of 3-acylindoles, see: (a) Curtin, M. L.; Davidsen, S. K.; Heyman, H. R.; Garland, R. B.; Sheppard, G. S.; Florjancic, A. S.; Xu, L.; Carrera, G. M., Jr.; Steinman, D. H.; Trautmann, J. A.; Albert, D. H.; Magoc, T. J.; Tapang, P.; Rhein, D. A.; Conway, R. G.; Luo, G.; Denissen, J. F.; Marsh, K. C.; Morgan, D. W.; Summers, J. B. *J. Med. Chem.* **1998**, *41*, 74. (b) Lehr, M. *J. Med. Chem.* **1997**, *40*, 2694. (c) Eissenstat, M. A.; Bell, M. R.; D'Ambra, T. E.; Alexander, E. J.; Daum, S. J.; Ackerman, J. H.; Gruett, M. D.; Kumar, V.; Estep, K. G.; Olefirowicz, E. M.; Wetzel, J. R.; Alexander, M. D.; Weaver, J. D.; Haycock, D. A.; Luttinger, D. A.; Casiano, F. M.; Chippari, S. M.; Kuster, J. E.; Stevenson, J. I.; Ward, S. J. *J. Med. Chem.* **1995**, *38*, 3094. (d) D'Ambra, T. E.; Estep, K. G.; Bell, M. R.; Eissenstat, M. A.; Josef, K. L.; Ward, S. J.; Haycock, D. A.; Baizman, E. R.; Casiano, F. M.; Beglin, N. C.; Chippari, S. M.; Grego, J. D.; Kullnig, R. K.; Daley, G. T. *J. Med. Chem.* **1992**, *35*, 124. (e) Bell, M. R.; D'Ambra, T. E.; Kumar, V.; Eissenstat, M. A.; Herrmann, J. L., Jr.; Wetzel, J. R.; Rosi, D.; Philion, R. E.; Daum, S. J.; Hlasta, D. J.; Kullnig, R. K.; Ackerman, J. H.; Haubrich, D. R.; Luttinger, D. A.; Baizman, E. R.; Miller, M. S.; Ward, S. J. *J. Med. Chem.* **1991**, *34*, 1099.

(11) For a kinetic study on the substituent effects on the acid hydration of alkynes, see: Allen, A. D.; Chiang, Y.; Kresge, A. J.; Tidwell, T. T. *J. Org. Chem.* **1982**, *47*, 775.

(12) Quantum mechanical calculations (PC Spartan Pro 1.0) indicated that the addition of water to acetylenic moiety of **3** should occur with high regioselectivity to give 3-acylindole derivatives.

(13) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437.

(14) Rao, M. L. N.; Periasamy, M. *Synth. Commun.* **1995**, *25*, 2295.

(15) Damle, S. V.; Seomoon, D.; Lee, P. H. *J. Org. Chem.* **2003**, *68*, 7085.

(16) Li, L.-S.; Wu, Y.-L. *Tetrahedron Lett.* **2002**, *43*, 2427.

TABLE 1. Ligands, Bases, Solvents, and Temperature in the Palladium-Catalyzed Reaction of *o*-(Phenylethynyl)trifluoroacetanilide 1a with 1-Iodophenylacetylene 2a and 1-Bromophenylacetylene 2b[a]

entry	2	Pd(0)	ligand	base	solvent	T (°C)	time (h)	yield % of **3a**[b]	yield % of **5a**[b]	yield % of **6a**[b]
1	**2a**	$Pd_2(dba)_3$	P(*o*-tol)$_3$	K_2CO_3	DMSO	40	40	19	tr	
2	**2a**	$Pd_2(dba)_3$	P(*o*-tol)$_3$	K_2CO_3	DMSO	60	21	28	50	
3	**2a**	$Pd_2(dba)_3$	P(2-furyl)$_3$	K_2CO_3	DMSO	60	2	20	60	
4	**2a**	$Pd_2(dba)_3$	P(*o*-tol)$_3$	K_2CO_3	DMSO	80	2	24	71	
5	**2a**	$Pd(PPh_3)_4$		K_2CO_3	MeCN	80	1	26	18	45
6	**2a**	$Pd(PPh_3)_4$		Cs_2CO_3	MeCN	80	1	18	30	31
7	**2a**	$Pd(PPh_3)_4$		K_2CO_3	MeCN	100	1	24	19	40
8	**2b**	$Pd(PPh_3)_4$		K_2CO_3	DMSO	60	9	76		
9	**2b**	$Pd(PPh_3)_4$		K_2CO_3	DMF	60	6	78		
10	**2b**	$Pd(PPh_3)_4$		K_2CO_3	MeCN	60	16	78	tr	
11	**2b**	$Pd(PPh_3)_4$		Cs_2CO_3	MeCN	60	6	76	8	
12	**2b**	$Pd(OAc)_2$	PPh_3	K_2CO_3	MeCN	60	23	63[c]	10	

[a] Reactions were carried out on a 0.346 mmol scale, in 2 mL of solvent, under an argon atmosphere, using 1 equiv of **1**, 1.2 equiv of **2**, 0.05 equiv of [Pd], and 3 equiv of base. [b] Yields refer to isolated products. [c] $Pd(OAc)_2/PPh_3$ = 1:4.

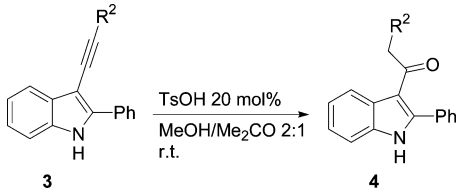
attempted. Indeed, the mixture of PPh_3 and $Pd(OAc)_2$ is known to generate spontaneously a zerovalent palladium complex that gives rise to oxidative addition reactions.[17] However, under these conditions the desired **3a** was isolated in lower yield (Table 1, entry 12) than with $Pd(PPh_3)_4$. Therefore, we initially selected $Pd(PPh_3)_4$ and Cs_2CO_3 in MeCN at 60 °C as satisfactory reaction conditions when we set out to explore the scope and limitations of this route to 3-alkynylindoles (see Table 2). However, Cs_2CO_3 did not provide as high reaction rate and comparable or better yields on a number of starting materials as with our model system. In some cases, K_2CO_3 provided better results (Table 2, compare entries 8 and 23 with, respectively, entries 7 and 22). In practice, the effectiveness of each base is to be evaluated each time.

Good to high yields of indole products have been usually obtained with 1-bromoarylalkynes bearing electron-donating or electron-withdrawing substituents. Alkyl groups bound to the alkyne fragment showed a tendency to give lower yields. In these cases, the use of $Pd_2(dba)_3$ and P(Bu-*t*)$_3$ as the ligand (added to the reaction mixture as the tetrafluoroborate salt)[18] can produce a significant increase of the yield (Table 2, compare entry 20 with entry 21). An interesting feature of the reaction is the formation of indoles containing free N−H pyrrole nuclei (the amide bond is broken during the reaction or/and the workup), avoiding troublesome and time-consuming deprotecting steps.

As to the mechanism, most probably the reaction proceeds through the basic steps of the aminopalladation−reductive elimination reaction:[1a] (a) reaction of **1** with a σ-alkynylpalladium intermediate [generated in situ via oxidative addition of the bromoalkyne to Pd(0)] to give a π-alkyne-σ-alkynylpalladium complex, (b) intramolecular nucleophilic attack of the nitrogen nucleophile across the activated carbon−carbon triple bond, and (c) reductive elimination of the resultant σ-indolyl-σ-alkynylpalladium intermediate that furnishes the indole product **3** and regenerates the active palladium catalyst.

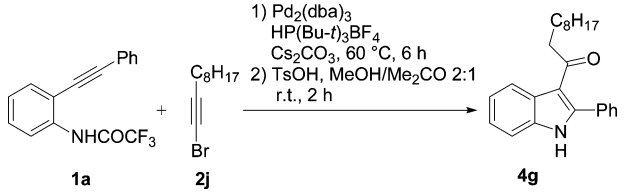
With a satisfactory procedure in hand for the preparation of 3-alkynylindoles **3**, we next attempted their conversion into 3-acylindoles **4**. We were pleased to find

SCHEME 3



3 4

SCHEME 4



1a 2j 4g

that the reaction proceeded with very high regioselectivity and that **4** could be readily obtained from **3** in high yield at room temperature in the presence of catalytic amounts of TsOH[19] (Scheme 3). Our preparative results are summarized in Table 3. The presence of electron-withdrawing or electron-donating substituents in the C2-position (R^1) or in the alkyne moiety (R^2) does not influence the regioselectivity of the acid hydration. All of the substrates that we have investigated gave always 3-acylindoles as the sole reaction products.

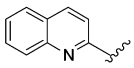
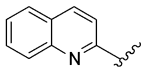
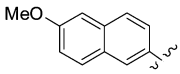
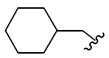
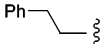
We have also developed a one-pot protocol for the preparation of 2-substituted 3-acylindoles from 1-bromoalkynes and *o*-alkynyltrifluoroacetanilides that omits the isolation of the alkynylindole intermediate. As an example, **4g** was obtained from **1a** and **2j** in 57% overall yield (Scheme 4).

Notably, the whole process mimics the formation of 3-acylindoles via the reaction of alkyl halides with *o*-alkynyltrifluoroacetanilides in the presence of carbon monoxide. Such a reaction was attempted by us with benzyl bromide and *o*-hexynyltrifluoroacetanilide, but the corresponding 3-acylindole was isolated in only 32% yield, the main product being the *N*-benzyl derivative of the starting alkyne generated via the competitive S_N reaction.

In conclusion, we have developed straightforward new routes for the preparation of 2-substituted 3-alkynylin-

(17) Amatore, C.; Jutand, A.; M'Barki, M. A. *Organometallics* **1992**, *11*, 3009.
(18) Netherton, M.; Fu, G. C, *Org. Lett.* **2001**, *3*, 4295.
(19) For a masterful review on the transition-metal-catalyzed addition of heteroatom-hydrogen bonds to alkynes, see: Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

TABLE 2. 2-Substituted 3-Alkynylindoles 3 via the Palladium-Catalyzed Reaction of o-Alkynyltrifluoroacetanilides 1 with 1-Bromoalkynes 2[a]

entry	R^1 **1**		R^2 **2**		t (h)	yield % of **3**[b]	
1	Ph	**1a**	Ph	**2b**	6	76[c]	**3a**
2	Ph	**1a**	Ph	**2b**	16	78[d]	**3a**
3	Ph	**1a**	*p*-$MeOC_6H_4$	**2c**	55	57[c]	**3b**
4	Ph	**1a**	*p*-$CHOC_6H_4$	**2d**	16	86[d]	**3c**
5	Ph	**1a**	*p*-$MeCOC_6H_4$	**2e**	7	65[c]	**3d**
6	Ph	**1a**	*p*-$MeCOC_6H_4$	**2e**	9	50[d]	**3d**
7	Ph	**1a**	*p*-$NO_2C_6H_4$	**2f**	8	58[c]	**3e**
8	Ph	**1a**	*p*-$NO_2C_6H_4$	**2f**	6	66[d]	**3e**
9	Ph	**1a**		**2g**	48	52[c]	**3f**
10	Ph	**1a**		**2g**	16	45[d]	**3f**
11	Ph	**1a**		**2h**	22	63[c]	**3g**
12	Ph	**1a**	*m*-NO_2-*p*-MeC_6H_3	**2i**	4	81[d]	**3h**
13	p-MeO-C_6H_4	**1b**	Ph	**2b**	8	75[c]	**3i**
14	p-MeO-C_6H_4	**1b**	*p*-$MeCOC_6H_4$	**2e**	6	73[c]	**3j**
15	p-MeO-C_6H_4	**1b**	*m*-NO_2-*p*-MeC_6H_3	**2i**	3	85[d]	**3k**
16	p-MeCO-C_6H_4	**1c**	Ph	**2b**	16	52[c]	**3l**
17	p-MeCO-C_6H_4	**1c**	*p*-$NO_2C_6H_4$	**2f**	8	59[c]	**3m**
18	CH_2OTHP	**1d**	Ph	**2b**	23	33	**3n**
19	CH_2OTHP	**1d**	*p*-$MeCOC_6H_4$	**2e**	5	56[d]	**3o**
20	Ph	**1a**	*n*-C_8H_{17}	**2j**	4	63[c,e]	**3p**
21	Ph	**1a**	*n*-C_8H_{17}	**2j**	30	40[d]	**3p**
22	Ph	**1a**	$Me_2C(OH)$	**2k**	8	50[c]	**3q**
23	Ph	**1a**	$Me_2C(OH)$	**2k**	30	62[d]	**3q**
24	Ph	**1a**		**2l**	7	53[c,e]	**3r**
25	Ph	**1a**		**2m**	5	40[c,e]	**3s**
26	p-MeO-C_6H_4	**1b**	*n*-C_8H_{17}	**2j**	2	43[c,e]	**3t**

[a] Reactions were carried out at 60 °C on a 0.346 mmol scale, in 2 mL of MeCN, under an argon atmosphere, using 1 equiv of **1**, 1.2 equiv of **2**, 0.05 equiv of $Pd(PPh)_4$, and 3 equiv of Cs_2CO_3 or K_2CO_3. [b] Yields refer to isolated products. [c] Cs_2CO_3. [d] K_2CO_3. [e] In the presence of 0.025 equiv of $Pd_2(dba)_3$ and 0.1 equiv of $HP(Bu\text{-}t)_3BF_4$.

TABLE 3. Conversion of 2-Substituted 3-Alkynylindoles 3 into 2-Substituted 3-Acylindoles 4[a]

entry	R^1, **1**	R^2, **2**		*t* (h)	yield % of **4**[b]	
1	*p*-$MeOC_6H_4$	Ph	**3i**	6	70	**4a**
2	*p*-$MeOC_6H_4$	*m*-NO_2-p-MeC_6H_3	**3k**	16	95	**4b**
3	Ph	*p*-$MeOC_6H_4$	**3b**	5	89	**4c**
4	*p*-$MeCOC_6H_4$	Ph	**3l**	7	68	**4d**
5	*p*-$MeOC_6H_4$	*n*-C_8H_{17}	**3t**	16	98	**4e**
6	CH_2OTHP	*p*-$MeCOC_6H_4$	**3o**	9	90	**4f**

[a] Reactions were carried out at room temperature on a 0,15 mmol scale, in 2 mL of a 2:1 MeOH/Me_2CO mixture using 0.2 equiv of TsOH. [b] Yields refer to isolated products.

doles and 2-substituted 3-acylindoles containing a free N−H pyrrole nucleus from readily available acyclic precursors. The process occurs under mild conditions and tolerates many important functional groups. As to 2-substituted 3-acylindoles, the present cyclization−hydration methodology can provide a useful approach to this important class of indole derivatives and a convenient alternative to classical methods based on the acylation of indoles such as the Friedel−Craft acylations,[20] Vilsmeier−Haack acylations,[21] and the reactions of indole salts with acyl chlorides.[22]

Acknowledgment. Work carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" supported by the Ministero dell'Istruzione, dell'Università e della Ricerca and by the University "La Sapienza". We also thank Mr. Gilles Lemiere for his dedication and contribution to this project within the Erasmus program.

Supporting Information Available: Experimental procedure and complete description of product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050517Z

(20) For some recent references, see: (a) Okauchi, T.; Itonaga, M.; Minami, T.; Owa, T.; Kitoh, K.; Yoshino, H. *Org. Lett.* **2000**, *2*, 1485. (b) Nicolaou, I.; Demopoulos, V. J. *J. Heterocycl. Chem.* **1998**, *35*, 1345. (c) Nakatsuka, S.; Teranishi, K.; Goto, T. *Tetrahedron Lett.* **1994**, *35*, 2699. (d) Tani, M.; Aoki, T.; Ito, S.; Matsumoto, S.; Hideshima, M.; Fukushima, K.; Nozawa, R.; Maeda, T.; Tashiro, M.; Yokoyama, Y.; Murakami, Y. *Chem. Pharm. Bull.* **1990**, *38*, 3261.

(21) For a recent reference, see: Allen, M. S.; Hamaker, L. K.; LaLoggia, A. J.; Cook, J. M. *Synth. Commun.* **1992**, *22*, 2077.

(22) For some recent references, see: (a) Yang, C. X.; Patel, H. H.; Ku, Y.-Y.; Shah, R.; Sawick, D. *Synth. Commun.* **1997**, *27*, 2125. (b) Faul, M. M.; Winneroski, L. L. *Tetrahedron Lett.* **1997**, *38*, 4749. (c) Davidsen, S. K.; Summers, J. B.; Albert, D. H.; Holms, J. H.; Heyman, H. R.; Magoc, T. J.; Conway, R. G.; Rhein, D. A.; Carter, G. W. *J. Med. Chem.* **1994**, *37*, 4423. (d) Macor, J. E.; Blank, D. H.; Fox, C. B.; Lebel, L. A.; Newman, M. E.; Post, R. J.; Ryan, K.; Schmidt, A. W.; Schulz, D. W.; Koe, B. K. *J. Med. Chem.* **1994**, *37*, 2509. (e) Bergman, J.; Venemalm, L. *Tetrahedron* **1990**, *46*, 6061.