JOC*Article*

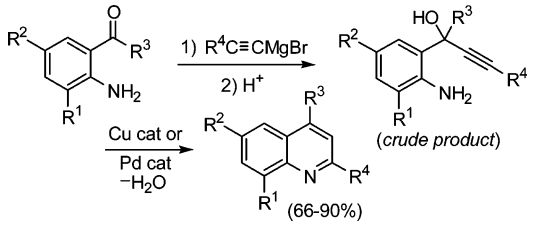
Novel and Convenient Synthesis of Substituted Quinolines by Copper- or Palladium-Catalyzed Cyclodehydration of 1-(2-Aminoaryl)-2-yn-1-ols

Bartolo Gabriele,*[,†] Raffaella Mancuso,[‡] Giuseppe Salerno,[‡] Giuseppe Ruffolo,[‡] and Pierluigi Plastina[‡]

Dipartimento di Scienze Farmaceutiche, Università della Calabria, 87036 Arcavacata di Rende (Cosenza), Italy, and Dipartimento di Chimica, Università della Calabria, 87036 Arcavacata di Rende (Cosenza), Italy

b.gabriele@unical.it

Received May 23, 2007



A general and convenient synthesis of substituted quinolines by regioselective copper- or palladium-catalyzed 6-*endo-dig* cyclization−dehydration of 1-(2-aminoaryl)-2-yn-1-ols is reported. The crude substrates were easily obtained by the Grignard reaction between the appropriate alkynylmagnesium bromide and 2-aminoaryl ketones and could be used without further purification for the subsequent cyclization step. Heteroannulation reactions were carried out in MeOH or DME as the solvent at 60 or 100 °C in the presence of $CuCl_2$ or PdX_2 (in conjunction with 10 equiv of KX, X = Cl, I) as the catalyst to afford the quinoline derivatives in good to excellent isolated yields based on starting 1-(2-aminoaryl)-2-yn-1-ols (66−90%).

Introduction

Quinolines are a very important class of heterocyclic compounds. The quinoline core is present in many biologically active natural products, in particular, alkaloids. Moreover, substituted quinolines are known to display a wide range of pharmacological activities, such as antiinflammatory,[1] antibacterial,[2] antiprotozoan,[3] antimalarial,[4] antiasthmatic,[5] antituberculosis,[6] anti-Alzheimer,[7] antihypertensive,[8] anthelmintic,[9] anti-HIV,[10] and anticancer activity.[11] In view of the remarkable importance of this class of heterocyclic compounds, during the last years many

† Dipartimento di Scienze Farmaceutiche.

‡ Dipartimento di Chimica.

(1) For recent examples, see: (a) Kym, P. R.; Kort, M. E.; Coghlan, M. J.; Moore, J. L.; Tang, R.; Ratajczyk, J. D.; Larson, D. P.; Elmore, S. W.; Pratt, J. K.; Stashko, M. A.; Falls, H. D.; Lin, C. W.; Nakane, M.; Miller, L.; Tyree, C. M.; Miner, J. N.; Jacobson, P. B.; Wilcox, D. M.; Nguyen, P.; Lane, B. C. *J. Med. Chem.* **2003**, *46*, 1016−1030. (b) Elmore, S. W.; Coghlan, M. J.; Anderson, D. D.; Pratt, J. K.; Green, B. E.; Wang, A. X.; Stashko, M. A.; Lin, C. W.; Tyree, C. M.; Miner, J. N.; Jacobson, P. B.; Wilcox, D. M.; Lane, B. C. *J. Med. Chem.* **2001**, *44*, 4481−4491. (c) Savini, L.; Chiasserini, L.; Pellerano, C.; Filippelli, W.; Falcone, G. *Farmaco* **2001**, *56*, 939−945. (d) Falk, S.; Goggel, R.; Heydasch, U.; Brasch, F.; Muller, K. M.; Wendel, A.; Uhlig, S. *Am. J. Resp. Crit. Care* **1999**, *160*, 1734−1742.

(2) For recent examples, see: (a) Narender, P.; Srinivas, U.; Ravinder, M.; Rao, B. A.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Rao, V. J. *Bioorg. Med. Chem.* **2006**, *14*, 4600−4609. (b) Holla, B. S.; Poojary, K. N.; Poojary, B.; Bhat, K. S.; Kumari, N. S. *Indian J. Chem. B* **2005**, *44*, 2114−2119. (c) Sadana, A. K.; Mirza, Y.; Aneja, K. R.; Prakash, O. *Eur. J. Med. Chem.* **2003**, *38*, 533−536. (d) Kumar, R. N.; Suresh, T.; Mohan, P. S. *Indian J. Chem. B* **2003**, *42*, 688−689. (e) Kidwai, M.; Bhushan, K. R.; Sapra, P.; Saxena, R. K.; Gupta, R. *Bioorg. Med. Chem.* **2000**, *8*, 69−72. (f) Fujita, M.; Chiba, K.; Tominaga, Y.; Hino, K. *Chem. Pharm. Bull.* **1998**, *46*, 787−796. (g) Kayirere, M. G.; Mahamoud, A.; Chevalier, J.; Soyfer, J. C.; Cremieux, A.; Barbe, J. *Eur. J. Med. Chem.* **1998**, *33*, 55−63.

(3) See, for example: (a) Tempone, A. G.; da Silva, A. C. M. P.; Brandt, C. A.; Martinez, F. S.; Borborema, S. E. T.; da Silveira, M. A. B.; de Andrade, H. F. *Antimicrob. Agents Chemother.* **2005**, *49*, 1076−1080. (b) Franck, X.; Fournet, A.; Prina, E.; Mahieux, R.; Hocquemiller, R.; Figadere, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3635−3638. (c) Sahu, N. P.; Pal, C.; Mandal, N. B.; Banerjee, S.; Raha, M.; Kundu, A. P.; Basu, A.; Ghosh, M.; Roy, K.; Bandyopadhyay, S. *Bioorg. Med. Chem.* **2002**, *10*, 1687−1694. (d) Chiari, E.; Oliveira, A. B.; Prado, M. A. F.; Alves, R. J.; Galvão, L. M. C.; Araujo, F. G. *Antimicrob. Agents Chemother.* **1996**, *40*, 613−615. (e) Fournet, A.; Barrios, A. A.; Munoz, V.; Hocquemiller, R.; Cave, A.; Bruneton, J. *Antimicrob. Agents Chemother.* **1993**, *37*, 859−863.

10.1021/jo071094z CCC: $37.00
Published on Web 07/26/2007

efforts have been devoted to the development of new regioselective synthetic methodologies for their production.[12] In particular, new synthetic strategies based on metal-catalyzed heteroannulation of acyclic precursors have attracted considerable attention, owing to the possibility to construct the quinoline ring with the desired substitution pattern in one step under mild conditions starting from readily available starting materials.[13]

We report here a general and convenient synthesis of substituted quinolines **3** through copper or palladium-catalyzed 6-*endo*-*dig* heteroannulation−dehydration of 1-(2-aminoaryl)-2-yn-1-ols **2**,[14,15] easily obtained by the Grignard reaction between the appropriate alkynylmagnesium bromide and 2-aminoaryl ketones **1** (Scheme 1). The intermediates **2** deriving from the first step could be used without further purification for the second step, thus facilitating the synthetic procedure.

Results and Discussion

We have recently reported several examples of copper- or palladium-catalyzed cycloisomerization reactions leading to heterocyclic derivatives starting from suitably functionalized alkyne derivatives.[16] In particular, we have reported a general methodology for the regioselective synthesis of substituted

(4) For recent examples, see: (a) Joshi, A. A.; Viswanathan, C. L. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2613−2617. (b) Joshi, A. A.; Narkhede, S. S.; Viswanathan, C. L. *Bioorg. Med. Chem. Lett.* **2006**, *15*, 73−76. (c) Dow, G. S.; Koenig, M. L.; Wolf, L.; Gerena, L.; Lopez-Sanchez, M.; Hudson, T. H.; Bhattacharjee, A. K. *Antimicrob. Agents Chemother.* **2004**, *48*, 2624−2632. (d) Portela, C.; Afonso, C. M. M.; Pinta, M. M. M.; Ramos, M. J. *Bioorg. Med. Chem.* **2004**, *12*, 3313−3321. (e) Ziegler, J.; Linck, R.; Wright, D. W. *Curr. Med. Chem.* **2001**, *8*, 171−189. (f) Billker, O.; Lindo, V.; Panico, M.; Etienne, A. E.; Paxton, T.; Dell, A.; Rogers, M.; Sinden, R. E.; Morris, H. R. *Nature* **1998**, *392*, 289−292. (g) Ismail, F. M. D.; Dascombe, M. J.; Carr, P.; Merette, S. A. M.; Rouault, P. *J. Pharm. Pharmacol.* **1998**, *50*, 483−492. (h) Go, M. L.; Ngiam, T. L.; Tan, A. L. C.; Kuaha, K.; Wilairat, P. *Eur. J. Pharm. Sci.* **1998**, *6*, 19−26.

(5) See, for example: (a) Heitsch, H. *Curr. Med. Chem.* **2002**, *9*, 913−928. (b) Buccellati, C.; Fumagalli, F.; Viappiani, S.; Folco, G. *Farmaco* **2002**, *57*, 235−242. (c) Dubé, D.; Blouin, M.; Brideau, C.; Chan, C. C.; Desmarais, S.; Ethier, D.; Falgueyret, J. P.; Friesen, R. W.; Girard, M.; Girard, Y.; Guay, J.; Riendeau, D.; Tagari, P.; Young, R. N. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1255−1260.

(6) For recent examples, see: (a) Nayyar, A.; Malde, A.; Jain, R.; Coutinho, E. *Bioorg. Med. Chem.* **2006**, *14*, 847−856. (b) Nayyar, A.; Jain, R. *Curr. Med. Chem.* **2005**, *12*, 1873−1886. (c) Monga, V.; Nayyar, A.; Vaitilingam, B.; Palde, P. B.; Jhamb, S. S.; Kaur, S.; Singh, P. P.; Jain, R. *Bioorg. Med. Chem.* **2004**, *12*, 6465−6472 (correction: **2005**, *13*, 1879). (d) Vangapamdu, S.; Jain, M.; Jain, R.; Kaur, S.; Singh, P. P. *Bioorg. Med. Chem.* **2004**, *12*, 2501−2508. (e) Jain, R.; Vaitilingam, B.; Nayyar, A.; Palde, P. B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1051−1054.

(7) See, for example: (a) Camps, P.; Gómez, E.; Muñoz-Torrero, D.; Badia, A.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **2001**, *44*, 4733−4736. (b) Camps, P.; El Achab, R.; Morral, J.; Muñoz-Torrero, D.; Badia, A.; Baños, J. E.; Vivas, N. M.; Barril, X.; Orozco, M.; Luque, F. J. *J. Med. Chem.* **2000**, *43*, 4657−4666. (c) Suzuki, T.; Usui, T.; Oka, M.; Suzuki, T.; Kataoka, T. *Chem. Pharm. Bull.* **1998**, *46*, 1265−1273.

(8) See, for example: (a) Muruganantham, N.; Sivakumar, R.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. *Biol. Pharm. Bull.* **2004**, *27*, 1683−1687. (b) Bradbury, R. H.; Allott, C. P.; Dennis, M.; Girdwood, J. A.; Kenny, P. W.; Major, J. S.; Oldham, A. A.; Ratcliffe, A. H.; Rivett, J. E.; Roberts, D. A.; Robins, P. J. *J. Med. Chem.* **1993**, *36*, 1245−1254.

(9) (a) Rossiter, S.; Peron, J. M.; Whitfield, P. J.; Jones, K. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4806−4808. (b) Kalluraya, B.; Sreenivasa, S. *Farmaco* **1998**, *53*, 399−404.

(10) See, for example: (a) Franck, X.; Fournet, A.; Prina, E.; Mahieux, R.; Hocquemiller, R.; Figadere, B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3635−3638. (b) Bénard, C.; Zouhiri, F.; Normand-Bayle, M.; Danet, M.; Desmaële, D.; Leh, H.; Mouscadet, J. F.; Mbemba, G.; Thomas, C. M.; Bonnenfant, S.; Le, Bret, M.; d'Angelo, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2473−2476. (c) Fakhfakh, M. A.; Fournet, A.; Prina, E.; Mouscadet, J. F.; Franck, X.; Hocquemiller, R.; Figadere, B. *Bioorg. Med. Chem.* **2003**, *11*, 5013−5023. (d) Fournet, A.; Mahieux, R.; Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadere, B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 891−894. (e) Zouhiri, F.; Desmaele, D.; d'Angelo, J.; Ourevitch, M.; Mouscadet, J. F.; Leh, H.; Le Bret, M. *Tetrahedron Lett.* **2001**, *42*, 8189−8192.

(11) See, for example: (a) Tsotinis, A.; Vlachou, M.; Zouroudis, S.; Jeney, A.; Timar, F.; Thurston, D. E.; Roussakis, C. *Lett. Drug Des. Discov.* **2005**, *2*, 189−192. (b) Martirosyan, A. R.; Rahim-Bata, R.; Freeman, A. B.; Clarke, C. D.; Howard, R. L.; Strobl, J. S. *Biochem. Pharmacol.* **2004**, *68*, 1729−1738. (c) Perzyna, A.; Klupsch, F.; Houssin, R.; Pommery, N.; Lemoine, A.; Hénichart, J. P. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2363−2365. (d) Abadi, A. H.; Brun, R. *Arzneimittel-Forsch.* **2003**, *53*, 655−663. (e) Charris, J.; Martinez, P.; Dominguez, J.; Lopez, S.; Angel, J.; Espinoza, G. *Heterocycl. Commun.* **2003**, *9*, 251−256. (f) Lamazzi, C.; Leonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Rees, C. W.; Besson, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2183−2185. (g) Osiadacz, J.; Kaczmarek, L.; Opolski, A.; Wietrzyk, J.; Marcinkowska, E.; Biernacka, K.; Radzikowski, C.; Jon, M.; Peczynska-Czoch, W. *Anticancer Res.* **1999**, *19*, 3333−3342. (h) Kaczmarek, L.; Peczynska-Czoch, W.; Osiadacz, J.; Mordarski, M.; Sokalski, W. A.; Boratynski, J.; Marcinkowska, E.; Glazman-Kusnierczyk, H.; Radzikowski, C. *Bioorg. Med. Chem. Lett.* **1999**, *7*, 2457−2464. (i) Peczynskaczoch, W.; Pognan, F.; Kaczmarek, L.; Boratynski, J. *J. Med. Chem.* **1994**, *37*, 3503−3510.

(12) For an excellent recent review, see: (a) Kouznetsov, V. V.; Méndez, L. Y. V.; Gómez, C. M. M. *Curr. Org. Chem.* **2005**, *9*, 141−161. For some very recent developments in the synthesis of quinolines, see: (b) Ichikawa, J.; Sakoda, K.; Moriyama, H.; Wada, Y. *Synthesis* **2006**, 1590−1598. (c) Couturier, M.; Le, T. *Org. Process Res. Dev.* **2006**, *10*, 534−538. (d) Janza, B.; Studer, A. *Org. Lett.* **2006**, *8*, 1875−1878. (e) Lin, X. F.; Cui, S. L.; Wang, Y. G. *Tetrahedron Lett.* **2006**, *47*, 3127−3130. (f) Chaudhuri, M. K.; Hussain, S. *J. Chem. Sci.* **2006**, *118*, 199−202. (g) Chabert, J. F. D.; Chatelain, G.; Pellet-Rostaing, S.; Bouchu, D.; Lemaire, M. *Tetrahedron Lett.* **2006**, *47*, 1015−1018. (h) Wang, G. W.; Jia, C. S.; Dong, Y. W. *Tetrahedron Lett.* **2006**, *47*, 1059−1063. (i) Tanaka, S. Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800−803. (j) Jia, C. S.; Zhang, Z.; Tu, S. J.; Wang, G. W. *Org. Biomol. Chem.* **2006**, *4*, 104−110. (k) Wu, J.; Xia, H. G.; Gao, K. *Org. Biomol. Chem.* **2006**, *4*, 126−129. (l) Morel, A. F., Larghi, E. L., Selvero, M. M. *Synlett* **2005**, 2755−2758. (m) Yadav, J. S.; Rao, P. P.; Sreenu, D.; Rao, R. S.; Kumar, V. N.; Nagaiah, K.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 7249−7253. (n) Rodriguez, J. G.; Rios, C. D. L.; Lafuente, A. *Tetrahedron* **2005**, *61*, 9042−9051. (o) Kosiecka, M., Maslankiewicz, A.; Maslankiewicz, M. J., *Heterocycles* **2005**, *65*, 1577−1588. (p) Zhang, X. X.; Campo, M. A.; Yao, T. L.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763−766. (q) Chelucci, G.; Manca, A.; Pinna, G. A. *Tetrahedron Lett.* **2005**, *46*, 767−770. (r) Karthikeyan, G.; Perumal, P. T. *J. Heterocycl. Chem.* **2004**, *41*, 1039−1041.

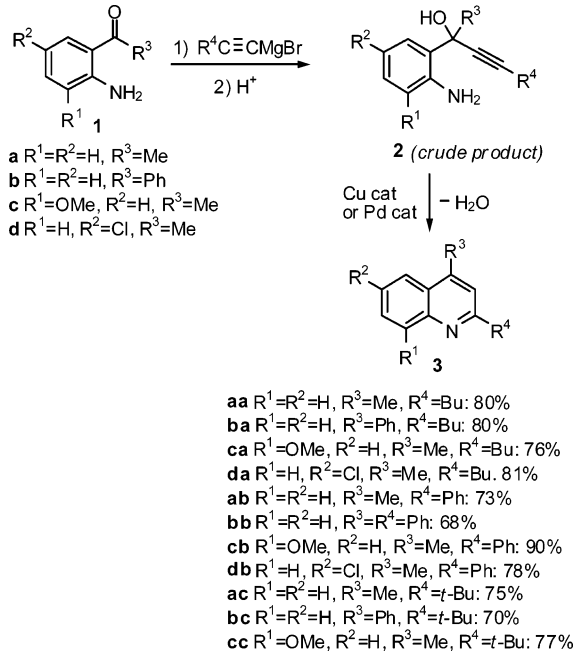
(13) For recent leading examples, see: (a) Jia, C. S.; Wang, G. W. *Lett. Org. Chem.* **2006**, *3*, 289−291. (b) Cho, C. S.; Ren, W. X.; Shim, S. C. *Bull. Kor. Chem. Soc.* **2005**, *26*, 2038−2040. (c) Bose, D. S.; Kumar, R. K. *Tetrahedron Lett.* **2006**, *47*, 813−816. (d) Wu, J.; Zhang, L.; Diao, T. N. *Synlett* **2005**, 2653−2657. (e) Cho, C. S.; Ren, W. X.; Shim, S. C. *Bull. Kor. Chem. Soc.* **2005**, *26*, 1286−1288. (f) Cho, C. S.; Seok, H. J.; Shim, S. C. *J. Heterocycl. Chem.* **2005**, *42*, 1219−1222. (g) Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, L.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454−6460. (h) Taguchi, K.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2005**, *46*, 4539−4542. (i) Martinez, R.; Brand, G. J.; Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **2005**, *46*, 3683−3686. (j) Arumugam, P.; Karthikeyan, G.; Atchudan, R.; Muralidharan, D.; Perumal, P. T. *Chem. Lett.* **2005**, *34*, 314−315. (k) De, S. K.; Gibbs, R. A. *Tetrahedron Lett.* **2005**, *46*, 1647−1649. (l) Igarashi, T.; Inada, T.; Sekioka, T.; Nakajima, T.; Shimizu, I. *Chem. Lett.* **2005**, *34*, 106−107.

(14) The formation of 6-chloro-2-cyclopropyl-4-trifluoromethylquinolin-5-ol from 3-amino-6-chloro-2-(3-cyclopropyl-1-hydroxy-1-trifluoromethylprop-2-ynyl)phenol, obtained in situ by deprotection of the corresponding *tert*-butyldimethylsilyl ether with TBAF, has been briefly mentioned in the literature as an undesired reaction, but no further experimental details (including the product yield) have been given for this reaction: (a) Markwalder, J. A.; Mutlib, D. D. C. A.; Cordova, B. C., Klabe, R. M.; Seitz, S. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 619−622. Formation of 6-chloro-2-cyclopropyl-4-trifluoromethylquinoline in 81% yield by refluxing a solution of 2-(2-amino-5-chlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol in chlorobenzene for 6 h has also been reported: (b) Choudhury, A.; Pierce, M. E.; Confalone, P. N. *Synth. Commun.* **2001**, *31*, 3707−3714.

(15) The iodocyclization of 1-(2-dimethylaminophenyl)-2-yn-1-ols to give 4-hydroxy-3-iodo-1,1-dimethyl-1,4-dihydroquinolinium iodides, which, upon heating, underwent formal loss of MeOH to give 3-iodo-1-methylquinolinium iodides has been recently reported: Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243−246.

(16) For a recent review, see: Gabriele, B.; Salerno, G.; Costa, M. *Synlett* **2004**, 2468−2483.

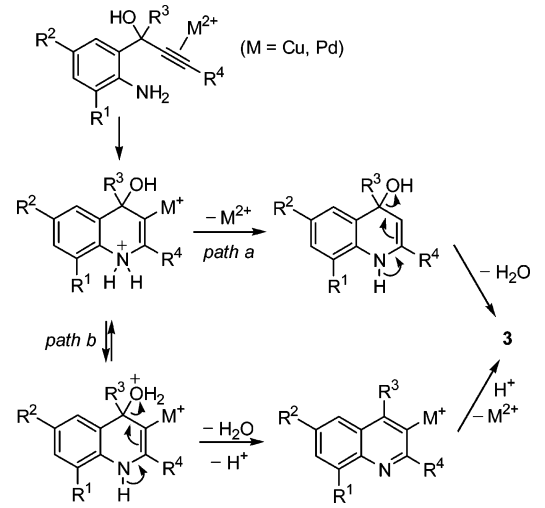
SCHEME 1



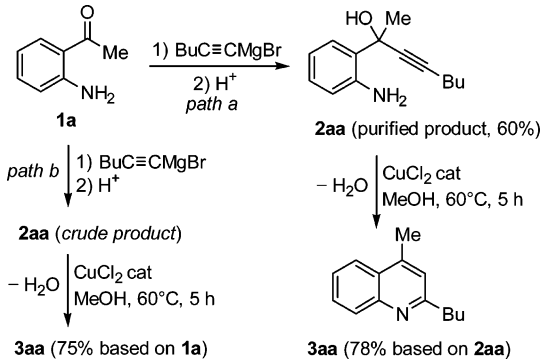
furans,[17] thiophenes,[18] and pyrroles[19] starting from (*Z*)-2-en-4-yn-1-ols, (*Z*)-2-en-4-yne-1-thiols, and (*Z*)-(2-en-4-ynyl)amines, respectively, through 5-*exo-dig* heteroannulation−aromatization promoted by PdX_2 in conjunction with KX (X = Cl, I) or by $CuCl_2$ as the catalytic system. We have also reported a divergent synthesis of (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans and 1*H*-isochromenes by PdI_2/KI-catalyzed 5-*exo-dig* or 6-*endo-dig*, respectively, cycloisomerization of 2-alkynylbenzyl alcohols.[20] On the basis of these results, we have investigated the possibility to synthesize substituted quinolines starting from 1-(2-aminoaryl)-2-yn-1-ols, through a metal-promoted 6-*endo-dig* cyclodehydration route, based on intramolecular nucleophilic attack of the $-NH_2$ group to the triple bond coordinated to the metal center followed by protonolysis and dehydration (Scheme 2, path *a*) or vice versa (path *b*).

The first substrate we used was 2-(2-aminophenyl)oct-3-yn-2-ol **2aa** ($R^1 = R^2 = H$, $R^3 = Me$, $R^4 = Bu$) obtained in ca. 60% isolated yield by the reaction between commercially available 2-aminoacetophenone **1a** and 1-hexynylmagnesium bromide. The reactivity of **2aa** was initially tested at 60 °C in MeOH as the solvent in the presence of 2 mol % of different catalytic systems, based on zinc, palladium, and copper. The results obtained are shown in Table S1 (see the Supporting Information). As can be seen, 2-butyl-4-methylquinoline **3aa** was selectively formed in all cases (entries 1−12), thus confirming the validity of our hypothesis. The best results in terms of substrate conversion rate and product selectivity were obtained with $CuCl_2$ as the catalyst: after 5 h reaction time, **3aa** was formed in 85% GLC yield at total substrate conversion (78% isolated, entry 12 and Scheme 3, path *a*). The reaction

SCHEME 2



SCHEME 3



did not occur in the absence of the metal catalyst, as confirmed by blank experiments (decomposition of the starting material to give unidentified chromatographically immobile materials was observed under these conditions, entry 13).

Using $CuCl_2$ as the catalyst, we next tested the reactivity of **2aa** in different solvents. The results, shown in Table S2, entries 14−19 (to be compared with entry 10 of Table S1, see the Supporting Information), clearly indicate MeOH as the solvent of choice for the reaction.

One drawback of this synthetic approach was related to the instability of **2aa** during the purification procedures, which in several cases caused its partial decomposition after column chromatography.[21] However, we have found that the cyclization reaction worked nicely even on the crude product, which also facilitated the synthetic protocol (see Experimental Section for details). Thus, when crude **2aa** was let to react under the same conditions of entry 12, quinoline **3aa** was obtained in 75% isolated yield based on starting 2-aminoacetophenone **1a** (Table 1, entry 20, and Scheme 3, path *b*). It is worth noting that this yield was considerably higher with respect to the overall yield obtained using pure **2aa** (47% isolated yield based on **1a**, Scheme 3, path *a*).

The generality of the process was then verified by varying the nature of substituents R^1 and R^2 (on the aromatic ring), R^3 (at the benzylic position), and R^4 (on the triple bond) (Scheme 1). The results are shown in Table 1. As can be seen, in most

(17) (a) Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* **1999**, *64*, 7687−7692. (b) Gabriele, B.; Salerno, G. *Chem. Commun.* **1997**, 1083−1084.

(18) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351−352.

(19) (a) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853−7861. (b) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. R. *Tetrahedron Lett.* **2001**, *42*, 1339−1341.

(20) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251−6259.

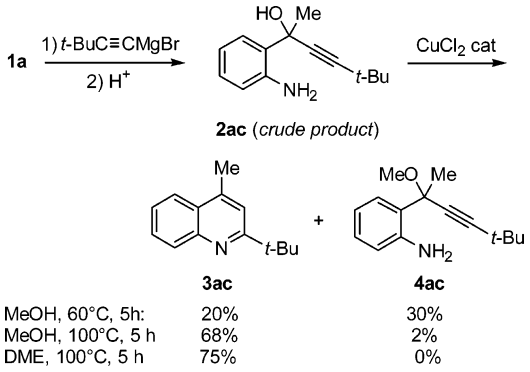
(21) Unidentified chromatographically immobile materials were formed as a result of decomposition.

TABLE 1. Synthesis of Substituted Quinolines 3 by Cyclodehydration of Crude 1-(2-Aminophenyl)-2-yn-1-ols 2, Obtained by the Reaction between $R^4C{\equiv}CMgBr$ and 2-Aminoaryl Ketones 1 in the Presence of $CuCl_2$ as Catalyst[a]

entry	1	R^1	R^2	R^3	R^4	2	T (°C)	3	yield of 3[b] (%)
20	**1a**	H	H	Me	Bu	**2aa**	60	**3aa**	75
21	**1a**	H	H	Me	Bu	**2aa**	100	**3aa**	80
22	**1b**	H	H	Ph	Bu	**2ba**	60	**3ba**	80
23	**1c**	OMe	H	Me	Bu	**2ca**	60	**3ca**	60
24	**1c**	OMe	H	Me	Bu	**2ca**	100	**3ca**	76
25	**1d**	H	Cl	Me	Bu	**2da**	60	**3da**	81
26	**1d**	H	Cl	Me	Bu	**2da**	100	**3da**	69
27	**1a**	H	H	Me	Ph	**2ab**	60	**3ab**	65
28	**1a**	H	H	Me	Ph	**2ab**	100	**3ab**	73
29	**1b**	H	H	Ph	Ph	**2bb**	60	**3bb**	63
30	**1b**	H	H	Ph	Ph	**2bb**	100	**3bb**	68
31	**1c**	OMe	H	Me	Ph	**2cb**	60	**3cb**	72
32	**1c**	OMe	H	Me	Ph	**2cb**	100	**3cb**	90
33	**1d**	H	Cl	Me	Ph	**2db**	60	**3db**	78
34	**1d**	H	Cl	Me	Ph	**2db**	100	**3db**	74
35	**1a**	H	H	Me	*t*-Bu	**2ac**	60	**3ac**	20[c]
36	**1a**	H	H	Me	*t*-Bu	**2ac**	100	**3ac**	68[d]
37[e]	**1a**	H	H	Me	*t*-Bu	**2ac**	100	**3ac**	75
38	**1b**	H	H	Ph	*t*-Bu	**2bc**	100	**3bc**	70
39[f]	**1c**	OMe	H	Me	*t*-Bu	**2cc**	100	**3cc**	77

[a] Unless otherwise noted, all reactions were carried out in MeOH (0.22 mmol of **1** per mL of MeOH, 9 mmol scale based on **1**) for 5 h in the presence of 2 mol % of $CuCl_2$. Conversion of **2** was quantitative in all cases. [b] Isolated yield based on starting **1**. [c] The reaction also led to the formation of 2-(1-methoxy-1,4,4-trimethylpent-2-ynyl)phenylamine **4ac** (30% isolated yield based on starting 2-aminoacetophenone **1a**). [d] The reaction also led to the formation of **4ac** (2% isolated yield based on starting **1a**). [e] The reaction was carried out in 1,2-dimethoxyethane (DME). [f] Reaction time was 2 h.

SCHEME 4



cases, better results in terms of product yield were obtained by working in a Schlenk flask at 100 °C rather than 60 °C. The benzylic position and the triple bond could be substituted with an alkyl as well as an aryl substituent, while electron-withdrawing as well as π-donating groups could be present on the aromatic ring.

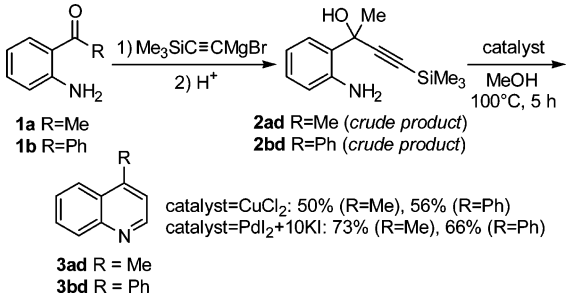
Interestingly, in the case of 2-(2-aminophenyl)-5,5-dimethylhex-3-yn-2-ol **2ac** ($R^1 = R^2 = H$, R^3= Me, R^4 = *tert*-Bu), the reaction, carried out under the same conditions of entry 20, led to 2-(1-methoxy-1,4,4-trimethylpent-2-ynyl)phenylamine **4ac** as the main reaction product (30% isolated yield based on starting 2-aminoacetophenone **1a**), together with smaller amounts of the expected 2-*tert*-butyl-4-methylquinoline **3ac** (20% isolated yield based on **1a**, entry 35 and Scheme 4). Clearly, this undesired reaction becomes competitive owing to the diminished reactivity of the sterically hindered triple bond. However, when the same reaction was carried out at 100 °C rather than 60 °C,

TABLE 2. Synthesis of 4-Substituted Quinolines 3ad and 3dd by Cu- or Pd-Catalyzed Cyclodehydration−Desilylation of Crude 1-(2-Aminophenyl)-2-yn-1-ols 2ad and 2dd, Obtained by the Reaction between TMS−C≡C−MgBr and 2-Aminophenyl Ketones 1a and 1d[a]

entry	1	R^1	R^2	R^3	R^4	2	catalyst	3[b]	yield of 3[c] (%)
40	**1a**	H	H	Me	TMS	**2ad**	$CuCl_2$	**3ad**	50
41	**1a**	H	H	Me	TMS	**2ad**	$PdCl_2$ + 10 KCl	**3ad**	69
42	**1a**	H	H	Me	TMS	**2ad**	PdI_2 + 10 KI	**3ad**	73
43	**1b**	H	H	Ph	TMS	**2bd**	$CuCl_2$	**3bd**	56
44	**1b**	H	H	Ph	TMS	**2bd**	$PdCl_2$ + 10 KCl	**3bd**	66
45	**1b**	H	H	Ph	TMS	**2bd**	PdI_2 + 10 KI	**3bd**	66

[a] Unless otherwise noted, all reactions were carried out in MeOH (0.22 mmol of **1** per mL of MeOH, 9 mmol scale based on **1**) at 100 °C for 5 h in the presence of 2 mol % of catalyst. Conversion of **2** was quantitative in all cases. [b] R^3 = H in the final product **3**. [c] Isolated yield based on starting **1**.

SCHEME 5



quinoline **3ac** became the main reaction product (68% isolated yield based on **1a**), **4ac** being formed in less than 2% isolated yield based on **1a** (entry 36 and Scheme 4). In a non-nucleophilic solvent such as 1,2-dimethoxyethane (DME), **3ac** was selectively obtained with a 75% isolated yield based on **1a** (entry 37 and Scheme 4). Under the same conditions of entry 36, other substrates bearing a *tert*-butyl group on the triple bond, such as 1-(2-aminophenyl)-4,4-dimethyl-1-phenylpent-2-yn-1-ol **2bc** ($R^1 = R^2 = H$, R^3 = Ph, R^4 = *t*-Bu), and 2-(2-amino-3-methoxyphenyl)-5,5-dimethylhex-3-yn-2-ol **2cc** (R^1 = OMe, $R^2 = H$, R^3 = Me, R^4 = *t*-Bu) afforded the corresponding quinolines **3bc** and **3cc**, respectively, in good isolated yield (70% and 77%, respectively) after 2−5 h reaction time (entries 38 and 39).

The cyclodehydration reaction could also be successfully applied to substrates bearing a trimethylsilyl group on the triple bond, such as 2-(2-aminophenyl)-4-trimethylsilanylbut-3-yn-2-ol **2ad** ($R^1 = R^2 = H$, R^3 = Me, R^4 = TMS). Under the same conditions of entry 21, this substrate was converted into 4-methylquinoline **3ad** ($R^1 = R^2 = R^4 = H$, R^3 = Me), ensuing from loss of the TMS group under the reaction conditions, in 50% isolated yield (Table 2, entry 40, and Scheme 5). Interestingly, a higher selectivity toward **3ad** (69−73%) could be obtained working in the presence of PdX_2 + 10 KX (X = Cl, I) as the catalytic system (entries 41 and 42 and Scheme 5). Similar results were observed in the case of 1-(2-aminophenyl)-1-phenyl-3-trimethylsilanylprop-2-yn-1-ol **2bd** ($R^1 = R^2$ =H, R^3 = Ph, R^4 = TMS) to give 4-phenylquinoline **3bd** ($R^1 = R^2 = R^4 = H$, R^3 = Ph) (entries 43−45 and Scheme 5).

Conclusions

We have developed a novel and practical synthesis of substituted quinolines through a two-step procedure involving

Grignard addition of alkynylmagnesium bromides to 2-aminoaryl ketones followed by regioselective copper- or palladium-catalyzed 6-*endo-dig* cyclodehydration of the corresponding 1-(2-aminophenyl)-2-yn-1-ols. The latter intermediates could be used without further purification for the subsequent cyclization step, thus further facilitating the synthetic procedure. The generality of the process has been verified by varying the nature of substituents on the aromatic ring as well as at the benzylic position and on the triple bond.

Experimental Section

Preparation of Substrates. 2-Aminoacetophenone **1a** and 2-aminobenzophenone **1b** were commercially available and were used as received. 2-Amino-3-methoxyacetophenone **1c** was prepared by nitration of commercially available 3-methoxyacetophenone followed by reduction, as described in the literature.[22] 2-Amino-5-chloroacetophenone **1d** was prepared by nitration of commercially available 3-chloroacetophenone followed by reduction, as described in the Supporting Information. Pure 2-(2-aminophenyl)oct-3-yn-2-ol **2aa** was prepared and characterized as described in the Supporting Information. Characterization data for quinolines **3** and 2-(1-methoxy-1-methylhept-2-ynyl)aniline **4ac** can also be found in the Supporting Information.

Cyclodehydration of 2-(2-Aminophenyl)oct-3-yn-2-ol 2aa to 2-Butyl-4-methylquinoline 3aa (Tables S1 and S2, See the Supporting Information). In a typical experiment, the catalyst (5.28×10^{-2} mmol) [in conjunction with KX (5.28×10^{-1} mmol) in the case of PdX_2, X = Cl or I] was added under nitrogen to a solution of pure **2aa** (574.0 mg, 2.64 mmol) in the anhydrous solvent (12.0 mL) (see Tables S1 and S2, see the Supporting Information) in a Schlenk flask. The resulting mixture was stirred under nitrogen at the temperature and for the time indicated in Tables S1 and S2. Solvent was evaporated, and the crude product purified by column chromatography on silica gel using 95:5 hexane-AcOEt as the eluent to give **3aa** as a yellow oil. The yields obtained in each experiment are reported in Tables S1 and S2.

General Procedure for the Synthesis of Quinolines 3 (Tables 1 and 2). To a suspension of Mg turnings (700.0 mg, 28.8 mmol) in anhydrous THF (2.0 mL), maintained under nitrogen and under reflux, was added pure EtBr (0.5 mL) to start the formation of the Grignard reagent. The remaining bromide was added dropwise (ca. 20 min) in THF solution (1.5 mL of EtBr in 15.0 mL of THF; total amount of EtBr added: 2.92 g, 26.8 mmol). The mixture was then allowed to reflux for additional 20 min. After cooling, the solution of EtMgBr thus obtained was transferred under nitrogen to a dropping funnel and was added dropwise to a solution of the 1-alkyne (26.8 mmol) in anhydrous THF (7.0 mL) at 0 °C with stirring. After additional stirring at 0 °C for 15 min, the mixture was allowed to warm up to room temperature, maintained at 50 °C for 2 h, and then used as such for the next step. 2-Amino ketone **1** (8.9 mmol) was dissolved under nitrogen in anhydrous THF (7.0 mL) and then added dropwise to the solution of the alkynylmagnesium bromide in THF (prepared as described above) at 50 °C under nitrogen. After stirring at 50 °C for 1 h ($R^1 = R^2 = H$, $R^3 =$ Me, $R^4 =$ Bu; $R^1 =$ OMe, $R^2 = H$, $R^3 =$ Me, $R^4 =$ Bu; $R^1 = H$, $R^2 =$ Cl, $R^3 =$ Me, $R^4 =$ Bu), 2 h ($R^1 =$ OMe, $R^2 = H$, $R^3 =$ Me, $R^4 =$ Ph; $R^1 = H$, $R^2 =$ Cl, $R^3 =$ Me, $R^4 =$ Ph; $R^1 =$ OMe, $R^2 = H$, $R^3 =$ Me, $R^4 =$ *t*-Bu; $R^1 = H$, $R^2 =$ Cl, $R^3 =$ Me, $R^4 =$ *t*-Bu; $R^1 = R^2 = H$, $R^3 =$ Me, $R^4 =$ Ph; $R^1 = R^2 = H$, $R^3 =$ Me, $R^4 =$ *t*-Bu; $R^1 = R^2 = H$, $R^3 =$ Me, $R^4 =$ TMS; $R^1 = R^2 = H$, $R^3 =$ Ph, $R^4 =$ *t*-Bu; $R^1 = R^2 = H$, $R^3 =$ Ph, $R^4 =$ TMS) or 3 h ($R^1 = R^2 = H$, $R^3 =$ Ph, $R^4 =$ Bu; $R^1 = R^2 = H$, $R^3 = R^4 =$ Ph), the mixture was cooled to room temperature. Saturated NH_4Cl was added with stirring to achieve weakly acidic pH. After additional stirring at room temperature for 15 min, AcOEt (ca. 20 mL) was added, and the phases were separated. The aqueous phase was extracted with AcOEt (3×30 mL), and the collected organic layers were washed with brine to neutral pH and eventually dried over Na_2SO_4. After filtration, the solvent was evaporated and crude products **2** used as such for the next step. $CuCl_2$ (24.0 mg, 1.79×10^{-1} mmol) [or PdX_2 (1.79×10^{-1} mmol) in conjunction with KX (1.79 mmol), X = Cl or I, see Tables 1 and 2] was added to a solution of crude **2** in anhydrous MeOH (40.5 mL) or DME (40.5 mL) (see Tables 1 and 2) in a Schlenk flask. The resulting mixture was stirred at the temperature and for the time indicated in Tables 1 and 2. Solvent was evaporated and the crude product purified by column chromatography on silica gel: **3aa** (yellow oil, 95:5 hexane−AcOEt); **3ba** (yellow oil, 95:5 hexane−AcOEt); **3ca** (yellow oil, 95:5 hexane−acetone); **3da** (yellow oil, 90:10 hexane−acetone); **3ab** (yellow solid, mp 65−67 °C, 95:5 hexane−AcOEt); **3bb** (yellow solid, mp 107−108 °C, 95:5 hexane−AcOEt); **3cb** (yellow solid, mp 96−97 °C, 90:10 hexane−acetone); **3db** (yellow solid, mp 89−90 °C, 99:1 hexane−acetone); **3ac** (yellow oil, 95:5 hexane−AcOEt); **3bc** (colorless solid, mp 86−87 °C, 95:5 hexane−acetone); **3cc** (yellow oil, 95:5 hexane−acetone); **3ad** (yellow oil, 90:10 hexane−acetone); **3bd** (yellow solid, mp 61−62 °C, 90:10 hexane−acetone). The yields obtained in each experiment are reported in Tables 1 and 2.

Acknowledgment. This work was supported by the Ministero dell'Università e della Ricerca (Progetto di Ricerca di Interesse Nazionale PRIN 2006031888, Roma, Italy) and by the Consorzio Interuniversitario Nazionale "Metodologie e Processi Innovativi di Sintesi" (CINMPIS, Bari, Italy) for a fellowship grant to P.P.

Supporting Information Available: Tables S1 and S2, general experimental methods, preparation and characterization of **1c**, **1d**, and **2aa**, characterization data, and copies of ^1H and ^{13}C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

JO071094Z

(22) It is interesting to note that the only mononitrated product obtained by nitration of 3-methoxyacetophenone was 3-methoxy-2-nitroacetophenone, as confirmed by ^1H NMR (see the Supporting Information). This product was obtained either by using the nitration procedure reported by Alford et al.[23] or by using the procedure recently reported by Robbins et al.[24] (see the Supporting Information for details). It is worth noting that in this latter case the authors have indicated the structure of the mononitrated product as 5-methoxy-2-nitroacetophenone rather than 3-methoxy-2-nitroacetophenone. The reduction of 3-methoxy-2-nitroacetophenone to give 2-amino-3-methoxyacetophenone was carried out as described in ref 24.

(23) Alford, E. J., Irving, H.; Marsh, H. S.; Schofield, K. *J. Chem. Soc.* **1952**, 3009−3017.

(24) Robbins, R. J.; Laman, D. M.; Falvey, D. E. *J. Am. Chem. Soc.* **1996**, *118*, 8127−8135.