JOC*Note*

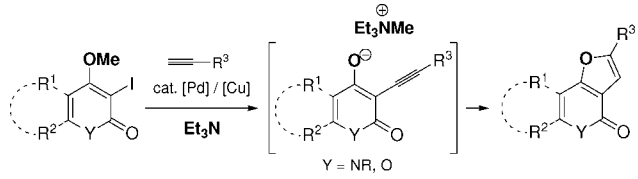
Et_3N-Induced Demethylation−Annulation of 3-Alkynyl-4-methoxy-2-pyridones and Structurally Related Compounds in the Synthesis of Furan-Fused Heterocycles

David Conreaux,[†] Sébastien Belot,[†] Philippe Desbordes,[‡] Nuno Monteiro,*[,†] and Geneviève Balme*[,†]

ICBMS, Institut de Chimie et Biochimie Moléculaire et Supramoléculaire, CNRS UMR 5246, Université Lyon 1, ESCPE Lyon. 43, Bd du 11 Novembre 1918, 69622 Villeurbanne, France, and Bayer CropScience, 14/20 rue Baizet, BP9163, 69623 Lyon Cedex 09, France

balme@univ-lyon1.fr; monteiro@univ-lyon1.fr

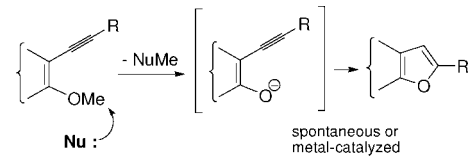
Received July 02, 2008



Various 3-iodo-4-methoxypyridin-2-ones and related pyrone and coumarin derivatives have been demonstrated as readily available precursors of 2-substituted furan-fused heterocycles by means of in situ sequential Sonogashira-acetylide coupling, dealkylation, and regioselective furan annulation reactions. A Et_3N-induced S_N2 process has been established that accounts for the dealkylation process.

The construction of furan-fused derivatives is an important endeavor in organic chemistry because of the abundance of these heterocyclic scaffolds in a large number of naturally occurring and designed molecules endowed with a wide array of biological properties.[1] In this area, the cycloisomerization of acetylenic compounds containing pendant oxygen functionalities offers a straightforward and atom-economical access to 2-substituted fused furans. These reactions generally require transition metal catalysis and may be viewed as proceeding through intramolecular 5-*endo-dig* attack of the nucleophilic substituent onto the coordinated alkynyl moiety.[2] However, while extensive work has been devoted to the cyclization of arylalkynol derivatives, investigations into the potential utility of arylalkynyl ethers as furan precursors are rare and have remained limited to the case of the easily accessible *o*-acetylenic anisoles. It has been shown that initial dealkylation steps may be achieved via nucleophilic substitution reactions under the reaction conditions to generate an intermediate *o*-acetylenic phenoxide, which subsequently undergoes cyclization (Scheme 1).[3,4]

SCHEME 1. Tandem Demethylation−Heteroannulation of *o*-Acetylenic Anisoles



For instance, Buckle showed in 1985 that lithium iodide was able to dealkylate (2-methoxyphenyl) ethynes in refluxing 2,4,6-trimethylpyridine, which resulted in the spontaneous[5] formation of benzo[*b*]furans.[3a] More recently, Hsung and co-workers demonstrated the synthesis of 2-amidobenzofurans via Rh-catalyzed demethylation−cyclization of *o*-anisole-substituted ynamides. It was suggested that adventitious water was likely the nucleophile that carried out the demethylation supposedly facilitated by prior complexation of the metal to the *o*-methoxy oxygen.[3b]

In a previous paper we demonstrated a versatile approach to 3,5-disubstituted 4-methoxypyridin-2-ones through site-selective Pd-catalyzed cross-coupling reactions. For instance, 3,5-diiodopyridin-2-one **1** has been shown to undergo selective Suzuki coupling reactions at the C-5 position to yield 5-arylpyridin-2-ones **2**, thus leaving the remaining C-3 halide free for further functionalization.[6] We now report that the latter 3-iodopyridin-2-ones can offer facile access to 7-arylfuro[3,2-*c*]pyridin-4-ones **3**, a rare structural core worthy of evaluation for biological properties,[7] by combining Sonogashira-acetylide coupling, dealkylation, and furan annulation reactions in a one-pot operation (Scheme 2).[8] We also provide clear evidence for a Et_3N-induced S_N2 dealkylation mechanism preceding anionic cyclization. Also included are applications of the method to other furan-fused heterocycles of biological relevance.

Our research originated from an unexpected observation made during Sonogashira cross-coupling experiments conducted on

[†] Université Lyon 1.
[‡] Bayer CropScience.

(1) For recent illustrations, see the following reviews:(a) McGuigan, C.; Balzarini, J. *Antiviral Res.* **2006**, *71*, 149. (b) Kim, S.; Salim, A. A.; Swanson, S. M.; Kinghorn, A. D. *Anti-Cancer Agents Med. Chem.* **2006**, *6*, 319. (c) Piggott, M. J. *Tetrahedron* **2005**, *61*, 9929. (d) Santana, L.; Uriarte, E.; Roleira, F.; Milhares, N.; Borges, F. *Curr. Med. Chem.* **2004**, *11*, 3239. (e) McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67.

(2) For recent contributions, see:(a) Kundu, N. G.; Pal, M.; Mahanty, J. S.; De, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2815. (b) Arcadi, A.; Cacchi, S.; Di Giuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2002**, 453. (c) Aucagne, V.; Amblard, F.; Agrofoglio, L. A. *Synlett* **2004**, 2406. (d) Robins, M. J.; Barr, P. J. *J. Med. Chem.* **2005**, *48*, 4690. (e) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (f) Belting, V.; Krause, N. *Org. Lett.* **2006**, *8*, 4489. (g) Venkataraman, S.; Barange, D. K.; Pal, M. *Tetrahedron Lett.* **2006**, *47*, 7317.

(3) (a) Buckle, D. R.; Rockell, C. J. M. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2443. (b) Oppenheimer, J.; Johnson, W. L.; Tracey, M. R.; Hsung, R. P.; Yao, P.-Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361. See also: (c) Godt, A.; Ünsal, Ö.; Roos, M. *J. Org. Chem.* **2000**, *65*, 2837. (d) Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334.

(4) For general reviews on dealkylation of ethers, see:(a) Ranu, B. C.; Bhar, S. *Org. Prep. Proced. Int.* **1996**, *28*, 371. (b) Tiecco, M. *Synthesis* **1988**, 749. (c) Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972. (d) Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.

(5) 2-Alkynylphenols are known to undergo facile cycloisomerization under alkaline conditions. For a leading reference, see: Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.

(6) Conreaux, D.; Bossharth, E.; Monteiro, N.; Desbordes, P.; Vors, J.-P.; Balme, G. *Org. Lett.* **2007**, *9*, 271.

(7) The related, naturally occurring 7-phenyldihydrofuro[3,2-*c*]pyridin-4-ones have been the focus of recent attention:(a) Snider, B. B.; Che, G *Org. Lett.* **2004**, *6*, 2877. (b) Clive, D. L. J.; Huang, X. *J. Org. Chem.* **2004**, *69*, 1872.

10.1021/jo8014038 CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/03/2008

SCHEME 2. Access to Furo[3,2-*c*]pyridin-4-ones via Site-Selective Functionalization of 3,5-Diiodopyridin-2-ones

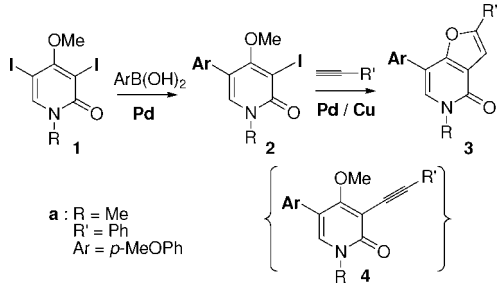
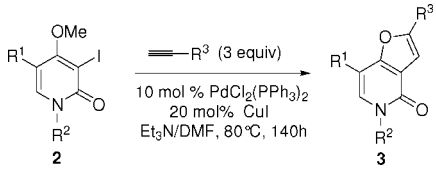


TABLE 1. Synthesis of 2-Substituted Furo[3,2-*c*]pyridin-4-ones[a]



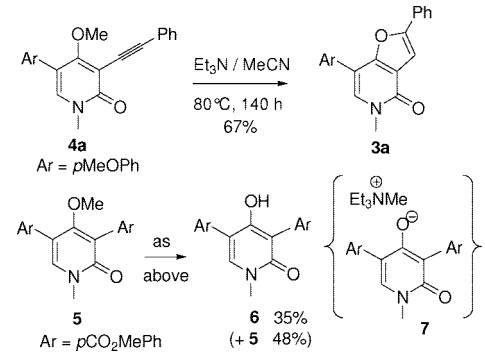
	R^1/R^2	R^3	product(s)/yield (%)[b]	
1	*p*-OMePh/Me (**2a**)	Ph	**3a**/63	(**4a**/22)
2	*p*-OMePh/Bn (**2b**)	Ph	**3b**/75	(**4b**/<5)
3	*p*-OMePh/Bn (**2b**)	*p*-CO_2MePh	**3c**/69	(**4c**/<5)
4	*p*-OMePh/Me (**2a**)	$SiMe_3$	**3d**/37[c]	(**4d**/23)
5	Ph/Me (**2c**)	Ph	**3e**/59[c]	(**4e**/37)
6	*p*-CO_2MePh/Me (**2d**)	*p*-OMePh	**3f**/56	(**4f**/11)
7	*p*-CO_2MePh/Me (**2d**)	Ph	**3g**/75	(**4g**/<5)

[a] All reactions were run on 0.4 mmol of the 3-iodopyridin-2-ones in 3 mL of Et_3N:DMF (2:1). [b] Isolated yields (single runs). Numbers in parentheses refer to yields of recovered 3-alkynylpyridin-2-one intermediates **4**. [c] Reaction performed in Et_3N/MeCN.

5-(4-methoxyphenyl)-pyridin-2-one **2a**. When the latter was reacted with phenylacetylene for reaction times longer than normally required to effect the cross-coupling reaction under classical Sonogashira conditions (cat. $PdCl_2(PPh_3)_2$, cat. CuI, Et_3N/MeCN, 50 °C),[9] small amounts of a side product, identified as furo[3,2-*c*]pyridin-4-one **3a**, were isolated in addition to the expected coupling product **4a**. Optimization of this model reaction required more forcing conditions than those described above and particularly higher temperatures (80 °C). DMF could also be used as a cosolvent to give essentially the same results. These new reaction conditions were found also to be effective for the synthesis of diversely substituted furopyridin-2-ones in moderate to good yields. 5-Aryl-3-iodopyridin-2-ones with both electron-donating and electron-withdrawing groups at the *para* position of the aromatic ring gave satisfying results. The acetylenic partners have also been expanded successfully to electron-rich and electron-poor aryl acetylenes, as well as TMS-acetylene (Table 1).

Further experiments have provided valuable insight into the mechanism of the furan-forming reaction. It was found that the process does not require metal catalysis and that Et_3N, used as cosolvent, was the sole reagent involved in the heteroannulation process. For instance, furopyridinone **3a** was isolated in 67% yield upon simple heating of 3-alkynylpyridin-2-one **4a** in

SCHEME 3. Et_3N-Induced Demethylation of 4-Methoxy-pyridin-2-ones



refluxing Et_3N/MeCN (2:1) for 140 h (Scheme 3).[10] Furthermore, indication that Et_3N was capturing the labile methyl group via S_N2 displacement prior to cyclization came from the observation that the methyl group of a 3,5-diarylpyridone lacking the triple bond was cleaved by triethylamine. For instance, 3,5-bisarylic 4-methoxy-1-methylpyridin-2-one **5** was treated by Et_3N in MeCN at 80 °C for 140 h. After solvent removal under vacuum, the crude reaction mixture was subjected to fractionation on silica gel to give 4-hydroxypyridin-2-one **6** (35% yield) and recovered **5** (48%) (Scheme 3).[11] In another experiment, the crude reaction mixture was dissolved in chloroform and extracted with water. The aqueous phase was then concentrated to dryness to leave a residual colorless gum containing an unstable pyridone derivative whose structure was tentatively assigned to triethylmethyl ammonium (TEMA) enolate **7** by NMR and mass spectroscopy.[12]

The capability of tertiary aliphatic amines to effect the cleavage of methyl ethers through nucleophilic displacement on the methyl group has been known for a long time. However, this interesting feature has not yet been developed into a synthetically useful dealkylation method. Indeed, the effectiveness of such a process generally requires drastic conditions and has been demonstrated mainly in the case of highly electron-deficient aromatics such as picryl ethers.[13,14] In light of the previous observations, we may propose the plausible, general mechanistic pathway described in Scheme 4 to explain the demethylation-cyclization process. Thus, nucleophilic displacement of the methyl group by triethylamine would generate a delocalized triethylmethyl ammonium enolate **8**. The latter would then undergo regioselective anionic 5-*endo-dig* cyclization to form the anionic furan intermediate **9**, which upon capture of a proton from water[15] would furnish the desired furo[3,2-*c*]pyridin-4-one together with the corresponding quaternary ammonium salt TEMA-OH (**10**). Interestingly, formation of the isomeric furo[3,2-*c*]pyridin-2-ones **11** was not observed.[16]

(8) So far, only one example of a similar process has been reported in the literature which refers to the formation in low yield of a furo[3,2-*c*]quinolin-4-one during the reaction of a 3-bromo-4-methoxyquinolin-2-one with a copper acetylide: Gaston, J. L.; Greer, R. J.; Grundon, M. F. *J. Chem. Res., Synop.* **1985**, 135.

(9) The coupling reaction is normally achieved in less than 16 h at 60°C to give **4a** in up to 81% isolated yield.

(10) It is worthy of note that the demethylation−cyclization reaction time may be significantly shortened by using microwave-induced heating. In a preliminary experiment a solution of alkynylpyridone **4b** in Et_3N/DMF (2:1) was submitted to microwave irradiation (CEM Discover apparatus; settings 120°C, 150W) during 6 h to give the corresponding furan derivative **3b** in 81% isolated yield.

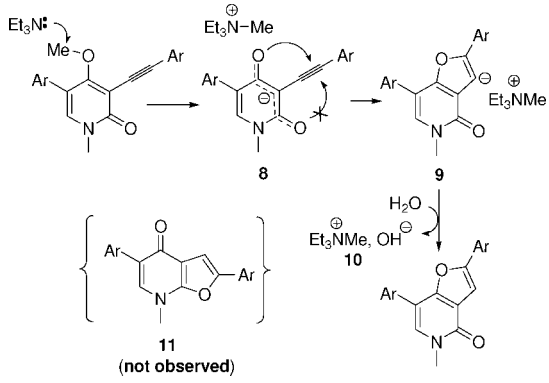
(11) The slow convertion rate may be explained by increased steric hindrance around the methoxy group.

(12) See Supporting information.

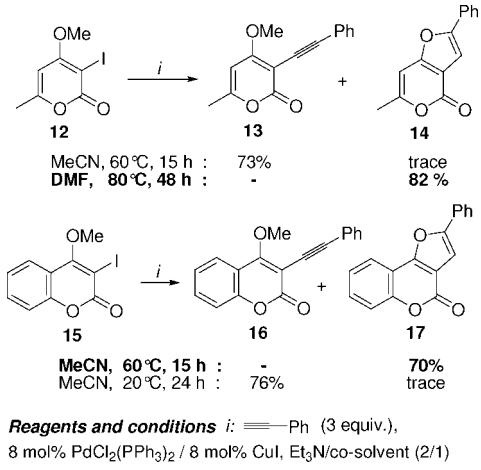
(13) (a) Burwell, R. L *Chem. Rev.* **1954**, 615. For a more recent leading reference, see: (b) Strauss, M.; Torres, R. *J. Org. Chem.* **1989**, *54*, 756.

(14) Scarce examples of nucleophilic O-dealkylations have also been reported to occur in the presence of primary and secondary aliphatic amines under high reaction temperatures (150−200°C):(a) Nishioka, H.; Nagasawa, M.; Yoshida, K. *Synthesis* **2000**, 243. (b) Shcherbakova, I.; Balandrin, M. F.; Fox, J.; Ghatak, A.; Heaton, W. L.; Conklin, R. L. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1557.

SCHEME 4. Plausible Mechanism for the Et_3N-Induced Dealkylation−Cyclization of 3-Alkynyl-4-alkoxypyridin-2-ones



SCHEME 5. One-Pot Synthesis of Furopyrone and Furocoumarin Derivatives



Next, the synthetic potential of the cascade coupling-cyclization methodology presented above led us to query whether other heterocyclic compounds structurally related to the 3-iodo-4-methoxypyridin-2-ones would behave in the same manner. We naturally turned our attention to the readily available 3-iodopyrone derivative **12**.[17] As a preliminary experiment, the Sonogashira coupling reaction of **12** with phenylacetylene was tested under classical reaction conditions (MeCN, 60 °C, 15 h), which allowed the isolation of 3-alkynyl-2-pyrone **13** in 73% yield (Scheme 5). Gratifyingly, when the same reaction was run at 80 °C in DMF as cosolvent, complete in situ conversion of the intermediate alkyne into furo[3,2-*c*]pyran-4-one **14**[18] (82% isolated yield) was achieved in 48 h. Encouraged by this interesting result, we then focused on expanding the protocol to include the easily accessible 3-iodo-4-methoxycoumarin **15** owing to the biological importance of furo[3,2-*c*]coumarins as well as the structurally related dihydrofurocoumarins and coumestans.[19] Interestingly, reaction of iodocoumarin **15** with phenylacetylene in MeCN at 60 °C under Sonogashira conditions did not allow isolation of the acetylenic coumarin **16** but instead led directly to the desired furocoumarin **17** within 15 h (70% isolated yield). It is worthy of note that the Sonogashira coupling product **16** may be obtained in up to 76% isolated yield by performing the coupling reaction at room temperature.

This preliminary result holds promise as an efficient, straightforward entry to furo[3,2-*c*]coumarins that compares favorably to previous methods reported in the litterature.[20] Again, Et_3N was found to be responsible for the demethylation step. However, in contrast to what was observed in the pyridone series, additional experiments suggested that copper catalysis was occurring in the cyclization step. Indeed, when acetylenic coumarin **16** was heated at 60 °C for 24 h in a mixture of Et_3N/MeCN, furocoumarin **17** was produced in only 15% yield. The main reaction product turned out to be the stable quaternary ammonium enolate intermediate **18**, which could be isolated by extraction into water and characterized by FT-IR, NMR, and mass spectroscopy.[12] On the other hand, when the same reaction was performed in the presence of 10 mol % CuI, the desired furocoumarin was isolated in 69% yield after 15 h reaction time. A reasonable mechanism for the Cu-catalyzed furan formation would involve coordination of the triple bond by CuI[21] followed by nucleophilic attack of the enolate, forming copper intermediate **19**. The latter would be protonated by water present in the system as contaminant, regenerating CuI and producing the furan derivative (Scheme 6).

In conclusion, we have shown that 3-iodopyridin-2-ones can give easy access to 2-substituted furan derivatives through in situ sequential Sonogashira-acetylide coupling, dealkylation, and furan annulation reactions. As for the dealkylation process, we have provided evidence for a Et_3N-induced S_N2 mechanism. The successful participation of structurally related compounds like pyrone and coumarin derivatives prefigures future extensions of this chemistry to the synthesis of other bis-heterocyclic compounds of interest. Further work will take into account the necessity of shortening reaction times in the pyridone series for better efficiency, most probably by using microwave catalysis.

(15) Protonation may occur spontaneously due to the probable presence of water as contaminant in the system or during workup. When used as solvent, MeCN may also intervene as a proton source owing to the predictable high basicity of the furan 2-anion:Shen, K.; Fu, Y.; Li, J.-N.; Liu, L.; Guo, Q.-X. *Tetrahedron* **2007**, *63*, 1568.

(16) Previous investigations from the same laboratories have demonstrated the selective synthesis of furopyridones of type **11** through electrophilic annulation/dealkylation reactions of 4-alkoxy-3-alkynyl-2-pyridones:(a) Bossharth, E.; Desbordes, P.; Monteiro, N.; Balme, G *Org. Lett.* **2003**, *5*, 2441. (b) Aillaud, I.; Bossharth, E.; Conreaux, D.; Desbordes, P.; Monteiro, N.; Balme, G. *Org. Lett.* **2006**, *8*, 1113.

(17) Cerezo, S.; Moreno-Mañas, M.; Pleixats, R. *Tetrahedron* **1998**, *54*, 7813.

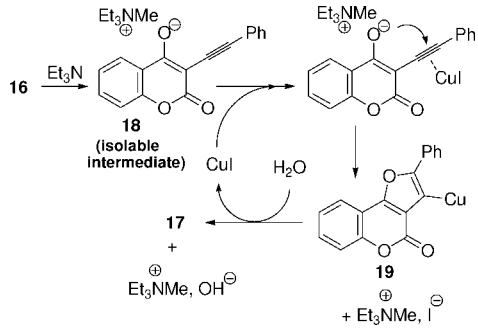
(18) This structure is rather uncommon but may be found in natural products: (a) Wang, Y.; Shang, X.-Y.; Wang, S.-J.; Mo, S.-Y.; Li, S.; Yang, Y.-C.; Ye, F.; Shi, J.-G.; He, L. *J. Nat. Prod.* **2007**, *70*, 296. (b) Lee, I.-K.; Yun, B.-S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2376.

(19) Furocoumarins:(a) Wang, X.; Nakagawa-Goto, K.; Kozuka, M.; Tokuda, H.; Nishino, H.; Lee, K.-H. *Pharm. Biol.* **2006**, *44*, 116. (b) Mulholland, D. A.; Iourine, S. E.; Taylor, D. A. H.; Dean, F. M. *Phytochemistry* **1998**, *47*, 1641. Dihydrofurocoumarins: (c) Motai, T.; Kitanaka, S. *Chem. Pharm. Bull.* **2004**, *52*, 1215. (d) Lee, Y. R.; Kim, B. S.; Wang, H. C *Tetrahedron* **1998**, *54*, 12215. Coumestans: (e) Pôças, E. S. C.; Lopes, D. V. S.; da Silva, A. J. M.; Pimenta, P. H. C.; Leitão, F. B.; Netto, C. D.; Buarque, C. D.; Brito, F. V.; Costa, P. R. R.; Noël, F. *Bioorg. Med. Chem.* **2006**, *14*, 7962. (f) da Silva, A. J. M.; Melo, P. A.; Silva, N. M. V.; Brito, F. V.; Buarque, C. D.; de Souza, D. V.; Rodrigues, V. P.; Pocas, E. S. C.; Noel, F.; Albuquerque, E. X.; Costa, P. R. R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 283.

(20) In many cases, mixtures of isomeric furo[3,2-*c*]coumarins and furo[3,2-*b*]chromones have been previously obtained:(a) Lee, Y. R.; Suk, J. Y. *Tetrahedron* **2002**, *58*, 2359. (b) Tollari, S.; Palmisano, G.; Cenini, S.; Cravotto, G.; Giovenzana, G. B.; Penoni, A. *Synthesis* **2001**, 735. (c) Kobayashi, K.; Sakashita, K.; Akamatsu, H.; Tanaka, K.; Uchida, M.; Uneda, T.; Kitamura, T.; Morikawa, O.; Konishi, H. *Heterocycles* **1999**, *51*, 2881. (d) Lee, Y. R.; Byun, M. W.; Kim, B. S. *Bull. Korean Chem. Soc.* **1998**, *19*, 1080. (e) Lee, Y. R.; Kim, B. S.; Wang, H. C. *Tetrahedron* **1998**, *54*, 12215. For a recent, selective approach to furo[3,2-*c*]coumarins, see: (f) Cheng, G.; Hu, Y. *Chem. Commun.* **2007**, 3285.

(21) Yamamoto, Y. *J. Org. Chem.* **2007**, *72*, 7817.

SCHEME 6. Working Mechanism for the Et_3N/CuI-Induced Dealkylation−Cyclization of 3-Alkynylcoumarin 16



Experimental Section

Typical Representative Procedures for Sonogashira-Acetylide Coupling/Annulation Reactions. 7-(4-Methoxy)phenyl-5-methyl-2-phenylfuro[3,2-*c*]pyridin-4(5*H*)-one 3a. A mixture of 3-iodopyridin-2-one **2a** (74.2 mg, 0.2 mmol), phenylacetylene (61.3 mg, 0.6 mmol), $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol), and CuI (7.6 mg, 0.04 mmol) was dissolved in DMF (1 mL) and TEA (2 mL) in a glass tube fitted with a Teflon screw seal. The reactor was flushed with nitrogen, and the reaction mixture was left to stir at 80 °C for 140 h and then concentrated under reduced pressure. The crude material so obtained was purified via column chromatography on silica gel using acetone/CH_2Cl_2 (1:9) as eluent to give 41.7 mg (63%) of **3a** as a solid. Mp 190−194 °C. IR (KBr): 3059, 1773, 1713, 1656 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.66 (s, 3H), 3.87 (s, 3H), 7.02 (dd, J = 6.8 and 2.0 Hz, 2H), 7.24 (s, 1H), 7.25 (s, 1H), 7.30−7.44 (m, 3H), 7.63 (dd, J = 6.8 and 2.0 Hz, 2H), 7.72−7.75 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.5, 55.7, 102.4, 111.0, 114.7, 118.3, 124.8, 125.4, 128.9, 129.2, 130.0, 132.4, 155.3, 157.2, 159.2, 159.7. HRMS (ESI): MH^+, 332.1280; calcd for $C_{21}H_{17}NO_3$, 332.1287.

2-Phenyl-4*H*-furo[3,2-*c*][1]benzopyran-4-one 17. A mixture of 3-iodocoumarin **15** (60.4 mg, 0.2 mmol), phenylacetylene (61.3 mg, 0.6 mmol), $PdCl_2(PPh_3)_2$ (11.2 mg, 0.016 mmol), and CuI (3.0 mg, 0.016 mmol) was dissolved in MeCN (1 mL) and TEA (2 mL) in a glass tube fitted with a Teflon screw seal. The reactor was flushed with nitrogen, and the reaction mixture was left to stir at 60 °C for 15 h and then concentrated under reduced pressure. The crude material so obtained was purified via column chromatography on silica gel using AcOEt/petroleum ether (1:4) as eluent to give 36.7 mg (70%) of **17** as a solid. Mp 166−168 °C. Spectral properties (IR, NMR) identical to those reported previously.[20f] HRMS (ESI): MH^+, 263.0707; calcd for $C_{17}H_{11}O_3$, 263.0708.

Acknowledgment. This research was assisted financially by a grant to D.C. from Bayer CropScience and the Centre National de la Recherche Scientifique. Dr. D. Bouchu is acknowledged for mass spectrometric analyses and Prof. P. Renaud (University of Bern) for valuable discussions.

Supporting Information Available: Experimental procedures and characterization data for all compounds and copies of NMR spectra of furan-fused heterocyclic compounds **3a-g**, **14**, and **17** and ammonium enolate intermediates **7** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8014038