ORGANIC LETTERS

2002
Vol. 4, No. 19
3215−3218

Palladium-Promoted Cascade Reactions of Isonitriles and 6-Iodo-*N*-propargylpyridones: Synthesis of Mappicines, Camptothecins, and Homocamptothecins

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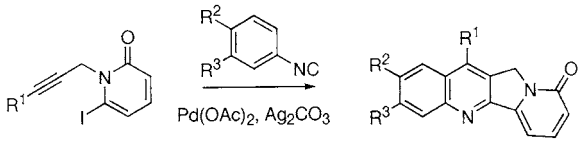
Received June 21, 2002

ABSTRACT



Ambient-temperature reactions of electron-rich aryl isonitriles with substituted 6-iodo-*N*-propargylpyridones in the presence of silver carbonate and palladium acetate produce 11*H*-indolizino[1,2-*b*]quinolin-9-ones in good to excellent yield. Experimental evidence suggests that the process occurs though organopalladium rather than radical intermediates. It is applied to synthesis analogues of mappicine and camptothecin, including the silatecans DB-67 and DB-91 (homo-DB-67).

Cascade radical reactions of aryl and alkenyl isonitriles have emerged as powerful tools for the synthesis of quinolines, indoles, and other heterocycles.[1] These reactions typically involve addition of a radical to an isonitrile to give an imidoyl radical, followed by one or more subsequent radical additions or cyclizations. In contrast, while transition-metal-mediated additions to isonitriles are well-known, most such processes result in direct 1,1-addition of a reagent to the isonitrile carbon,[2] and the possibility for making heterocycles[3] by cascade processes involving the isonitrile nitrogen substituents has not often been exploited.

Cascade radical reactions of aryl isonitriles **1** and 6-iodo-*N*-propargylpyridones **2** typically provide 11*H*-indolizino-[1,2-*b*]quinolin-9-ones **3** in about 40−60% yield in a single step (Scheme 1).[4] This ring system is the core of mappicine **4**,[5] camptothecin **5**,[6] and homocamptothecin **6**,[7] and we have made several hundred analogues of these molecules by cascade radical annulations in recent years.[8] Many of these camptothecin and homocamptothecin analogues are potent

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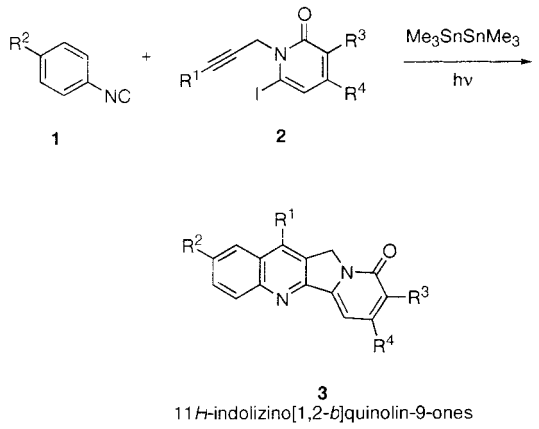
10.1021/ol026408d CCC: $22.00
Published on Web 08/20/2002

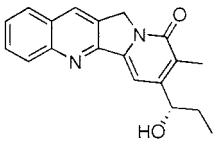
Scheme 1



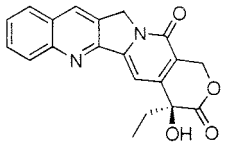
1 2

3
11*H*-indolizino[1,2-*b*]quinolin-9-ones

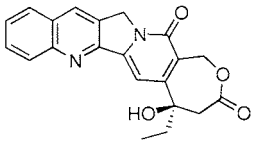
anticancer agents, and one of the most promising new compounds, DB-67 **7**, is currently in preclinical development.[9]



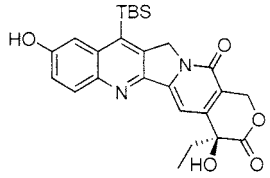
4
mappicine



5
(*S*)-camptothecin



6
(*R*)-homocamptothecin

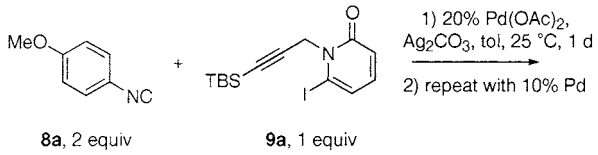


7
DB-67

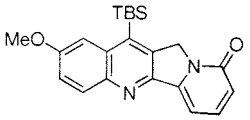
While the generality and simplicity of the cascade radical addition approach are nearly ideal for discovery chemistry, the reliance on stoichiometric quantities of tin reagents, with the attendant toxicity issues and separation problems,[10] is far from ideal for large scale synthesis. We report herein a palladium-catalyzed process that provides 11*H*-indolizino-[1,2-*b*]quinolin-9-ones from the same two precursors as the tandem radical process. The new process already functions well for small-scale preparations, and the results form the basis for the development of a practical large-scale method.

p-Methoxyphenylisonitrile **8a** and *N*-propargylpyridone **9a** were chosen as substrates for an initial survey of reaction conditions because the target product **10a** from this reagent pair has a substitution pattern similar to that of DB-67 **7**. Treatment of **8a** and **9a** with 10% $Pd(OAc)_2$, 20% Ph_3P, and Et_3N in MeCN at 80 °C gave only traces of the product **10a** as assayed by TLC analysis against an authentic sample (Scheme 2). In follow-up reactions, we varied the Pd catalysts, ligands, solvents, temperatures, and bases.[11] We learned that a phosphine ligand was not needed for the reaction. Toluene was found to be a suitable solvent, and the reaction occurred at room temperature. Addition of a base proved helpful, and among the bases tried, Ag_2CO_3 proved to be the best.

Scheme 2



8a, 2 equiv **9a**, 1 equiv



10a, 83%

In a typical reaction, 1 equiv of **9a**, 1.5 equiv of Ag_2CO_3, and 20% $Pd(OAc)_2$ were mixed in toluene, and then 2 equiv of isonitrile **8a** was slowly added at room temperature. A clean transformation occurred, and after 20 h, a mixture of product **10a** and starting iodopyridone **9a** in a 3:1 ratio was obtained. Various attempts to push the reaction to completion were not successful. Although excess isonitrile was used, its presence was not detected in the ^1H NMR spectrum of the product mixture obtained after removing insoluble materials. Once the reaction had stopped, addition of more isonitrile or Pd catalyst alone did not result in further conversion.

The reaction was finally driven to completion by a simple recycle process. After filtration to remove insoluble material

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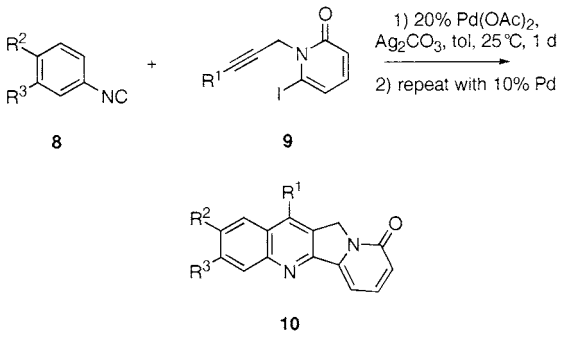
(11) Du, W. Ph.D. Thesis, University of Pittsburgh, 2002.

and evaporation of the solvent, the crude product was simply resubjected to the same conditions with reduced Pd catalyst loading (10%). After an additional 20 h, workup and purification by flash chromatography gave the polycyclic quinoline **10a** in 83% isolated yield. This product was identical to an authentic sample prepared under the ditin photolysis conditions.

The standard procedure with a single recycle was then applied to different iodo-*N*-propargylpyridones and substituted isonitriles, and the results of these experiments are summarized in Table 1. The substituent on the isonitrile

Table 1. Polycyclic Quinolines Prepared by Palladium-Promoted Cascade Reactions of *para*-Substituted Isonitriles and Iodopyridones



8 9 10

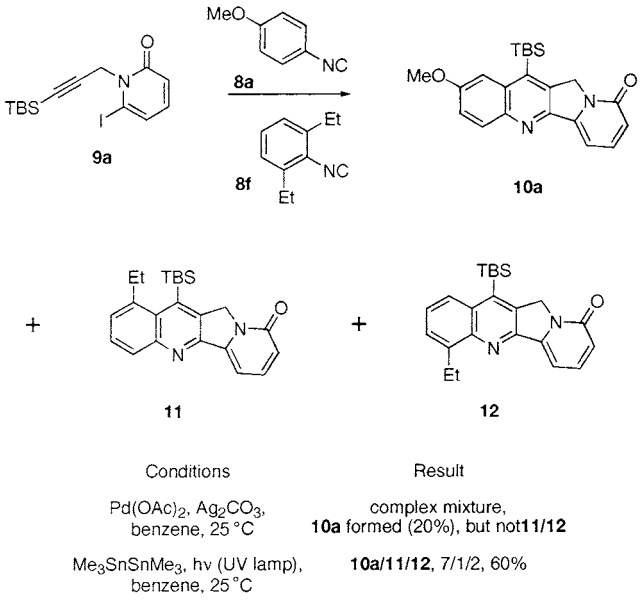
entry	isonitrile **8** (R^2, R^3)	iodopyridone **9** (R^1)	quinoline **10** (yield, %)[a]
1	**8a** (4-MeO)	**9b** (TES)	**10b** (66)
2	**8b** (4-BnO)	**9a** (TBS)	**10c** (92)
3	**8c** (4-Me_2N)	**9c** (TMS)	**10d** (67)
4	**8d** (4-Me)	**9a** (TBS)	**10e** (41)[b]
5	**8c** (4-Me_2N)	**9d** (^{t}Bu)	**10f** (41)
6	**8e** (3,4-diOMe)	**9a** (TBS)	**10g** (83)

[a] Isolated yield after flash chromatography. [b] Yield determined by ^{1}H NMR analysis, 40% of the starting iodopyridone was also present.

played an important role in the success of the reaction. Various electron-rich alkoxy (**8a**,**b**,**e**) and amino (**8c**) isonitriles gave good to excellent yields (entries 1−3), while *p*-tolyl isonitrile **8d** (entry 4) gave lower yield (41%) along with unreacted starting material **9a** (40%). Reaction of 3,4-methylenedioxyisonitrile **8e** with **9a** gave a single regioisomeric teracycle **10g** (83%). The same regioisomer **10g** was produced under standard ditin photolysis conditions but in only about half the yield. Both silyl and *tert*-butyl groups (entry 5) are acceptable on the terminus of the propargyl groups; however, an attempt to react a terminally unsubstituted propargyl pyridone failed to provide the product. Phenylisonitrile and isonitriles with electron-withdrawing groups only gave traces of tetracyclic products (results not shown). We also tested *N*-propargylchloropyridones and bromopyridones (not shown) but found that these were much less reactive.

The need for electron-rich isonitriles provides circumstantial evidence that the palladium-mediated reaction is not proceeding through the usual free-radical addition mechanism.[12] To provide additional evidence that radicals are not involved, we conducted the competition experiments shown in Scheme 3. Under palladium conditions, pyridone **9a** re-

Scheme 3



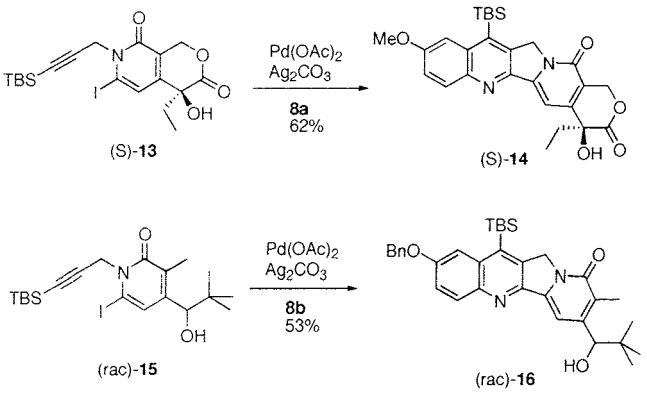
acts with *p*-methoxyphenylisonitrile **8a** (Scheme 2) but not 2,6-diethylphenylisonitrile **8f**. Under radical conditions ($Me_3SnSnMe_3$, benzene, sunlamp photolysis, 60−70 °C), **9a** reacts with both isonitriles; reaction with **8a** gives **10a** in 81% yield while reaction with **8f** gives a 0.9/1 mixture of regioisomers **11** and **12** in 79% yield.[13] We rationalized that if radicals were generated during a competition experiment then a mixture of three products should result. Indeed, a competitive experiment with **8a** and **8f** (4 equiv) promoted by irradiation with UV light (25 °C) in the presence of $Me_3SnSnMe_3$ produced **10a**, **11**, and **12** in a 7/1/2 ratio in 60% combined yield. In contrast, a competitive reaction under the palladium conditions but with benzene as the solvent to mimic the radical reaction gave a complex mixture containing **10a** (20% yield) but not **11** or **12**. These results suggest that radicals are not involved in the palladium process.

On the basis of the information provided by the model substrates, the reaction was then applied to camptothecin and mappicine analogues. *p*-Methoxyphenylisonitrile **8a** reacted with iodopyridone (*S*)-**13** to give camptothecin analogue (*S*)-**14** in 62% yield, and *p*-benzyloxyphenyl isonitrile **8b** reacted with iodopyridone *rac*-**15** to give mappicine analogue *rac*-**16** in 53% yield (Scheme 4).

(12) For examples of palladium-promoted or -initiated radical reactions, see: (a) Curran, D. P.; Chang, C.-T. *Tetrahedron Lett.* **1990**, *31*, 933. (b) Ryu, H.; Kreimerman, S.; Araki, F.; Nishitani, S.; Oderaotoshi, Y.; Minakata, S.; Komatsu, M. *J. Am. Chem. Soc.* **2002**, *124*, 3812.

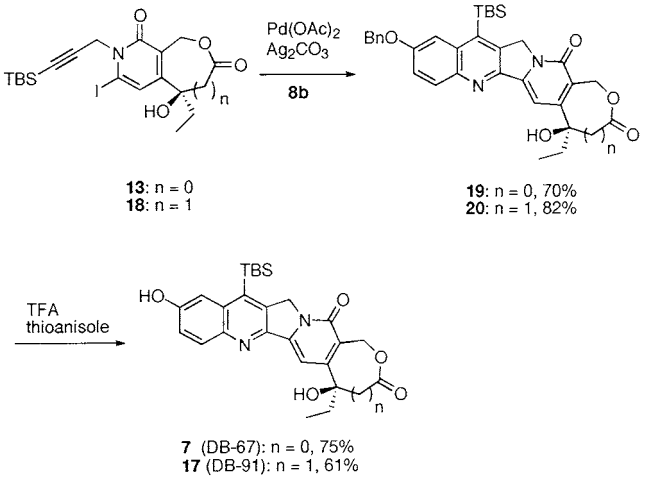
(13) Full details of radical reactions with 2,6-disubstituted aryl isonitriles will be described separately. Du, W.; Curran, D. P. Manuscript in preparation.

Scheme 4



To illustrate the practical utility of this process, we prepared DB-67 (**7**) and its homolog DB-91 (**17**).[14] Isonitrile **8b** reacted under the standard conditions with iodopyridones **13** and **18**[8e] to give **19** and **20** in 70% and 82% yield (Scheme 5). Treatment of **19** and **20** with TFA and thioanisole

Scheme 5



removed the benzyl ether protective group to give the desired products **7** and **17** in 75% and 61% yield. These yields are superior to those obtained on a small scale for the radical photolysis conditions. In addition, purification is easier, and the difficulties posed by scaling up the photolytic radical reactions should not be encountered in the palladium-promoted reactions.

The mechanism of the palladium-catalyzed reaction is not clear at this point. We speculate (Figure 1) that a palladium

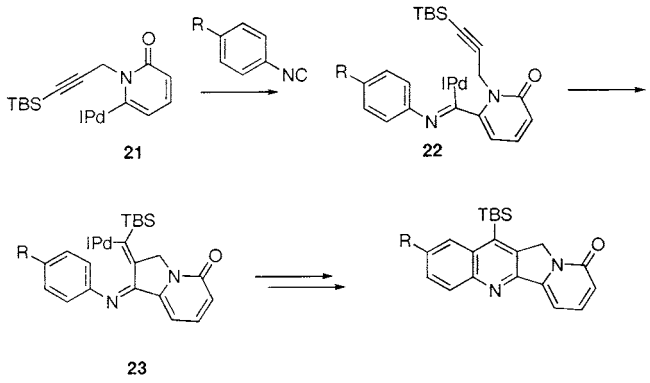


Figure 1. Possible series of steps involving organopalladium intermediates.

species, possibly already ligated to one or more isonitriles, inserts into the C−I bond of the iodopyridine to give **21**. Subsequent 1,1-addition to an isonitrile to give **22**, followed by intramolecular addition to the triple bond, gives a vinylpalladium species **23**. This species could cyclize by oxidative addition to an ortho CH bond followed by reductive elimination of a palladium hydride[15a] or by addition to the aromatic ring (or electrocyclization) followed by palladium hydride elimination.[15b] Reaction of the so-formed palladium hydride species with the base regenerates the starting low-valent palladium species (not shown). Silver carbonate may also ionize one or more of the palladium iodide intermediates.

In conclusion, we have developed a new Pd-promoted cascade reaction of electron-rich isonitriles and applied this to synthesis of polycyclic quinolines. While the reaction does not currently exhibit the scope of the cascade radical annulation with respect to the isonitrile substituent, it is convenient to conduct on small scale and produces some of the most important classes of camptothecin and homocamptothecin analogues in better yields than the radical process. Further improvements in reaction conditions including reducing the amount of palladium and eliminating the recycle could result in a practical large-scale process.

Acknowledgment. We thank the National Institute of Health for supporting this work. W.D. thanks the University of Pittsburgh for a Mellon Predoctoral Fellowship. We thank Drs. David Bom, Oscar de Frutos, and Thomas Isarno for preparing some intermediates used in this work.

Supporting Information Available: Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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