JOC Article

Sequential Amination/Annulation/Aromatization Reaction of Carbonyl Compounds and Propargylamine: A New One-Pot Approach to Functionalized Pyridines

Giorgio Abbiati,[†] Antonio Arcadi,*[,‡] Gabriele Bianchi,[‡] Sabrina Di Giuseppe,[‡] Fabio Marinelli,[‡] and Elisabetta Rossi[†]

Istituto di Chimica Organica "Alessandro Marchesini", Facoltà di Farmacia, Università degli Studi di Milano, Via Venezian, 21, 20133 Milano, Italy, and Dipartimento di Chimica, Ingegneria Chimica e Materiali, Facoltà di Scienze, Università di L'Aquila, Via Vetoio, 67010 Coppito(AQ), Italy

arcadi@univaq.it

Received May 29, 2003

A general one-pot synthesis of pyridines **4a**−**t** from the reaction of dialkyl acyclic/cyclic ketones **1a**−**i**, methyl, aryl/heteroaryl ketones **1m**−**r**, and aldehydes bearing α-hydrogens **1s**,**t** with propargylamine **2** is described. Gold and copper salts are efficient catalysts for the reaction of ketones with **2**. The formation of the pyridines **4** is suggested to proceed through the sequential amination of carbonyl compounds followed by regioselective *6-endo-dig* cyclization of the *N*-propargylenamine (*N*-propargyldienamine) intermediate **3(5)** and aromatization reaction. Whereas the preparation of linear polycyclic pyridine **4i** can be carried out by reacting cholestan-3-one **1i** with **2**, the angular polycyclic pyridine **4j** has been obtained starting from cholest-5-en-3-one **1j**. Selectivity of the reaction of polycyclic dicarbonyls **1k**,**l** with **2** has also been investigated.

Introduction

Pyridine derivatives have gained considerable attention due to their central role as versatile building bocks in the synthesis of natural products[1] and new materials with novel photo- or electrochemical or catalytic properties[2] and in the design of therapeutic agents.[3] In nature, the pyridine nucleus is found in the coenzyme vitamin B_6 family and in numerous alkaloids.[4] Practical synthesis of alkaloids depends on the existence of available methods to synthesize the functionalized pyridine nucleus.[5] In addition, low molecular weight heterocyclic molecules are ideal scaffolds for the high throughput synthesis of libraries of druglike compounds.[6] In particular, the efficient synthesis of libraries of highly substituted pyridines is important in the search for biologically active compounds for the pharmaceutical and agrochemical sectors. Selective activation or inhibition of a specific subclass of receptors is an important challenge in medicinal chemistry to design conformationally constrained compounds which exactly fit a single receptor subtype.[7] In this context, highly substituted pyridines have recently found applications as antiarteriosclerotics since they efficiently inhibit HMG-CoA reductase and cholesterol transport proteins.[8]

Although many synthetic routes to pyridines already exist, most methods are scarcely used by the lack of generality or selectivity, the harsh reactions conditions

* To whom correspondence should be addressed. Tel: +39 0862 433774. Fax: + 39 0862 433753.

[†] Università degli Studi di Milano.

[‡] Università di L'Aquila.

(1) Wang, Y.; Dong, X.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 3090−3098. Moody, C. J.; Hughes, R. A.; Thompson, S. P.; Alcaraz, L. *Chem. Commun.* **2002**, 1760−1761. Bach, T.; Heuser, S. *Synlett* **2002**, 2089−2091.

(2) Puglisi, A.; Benaglia, M.; Roncan, G. *Eur. J. Org. Chem.* **2003**, 1552−1558. Heller, M.; Schubert, U. S. *Eur. J. Org. Chem.* **2003**, 947−961. Skaff, H.; Emrick, T. *Chem. Commun.* **2003**, 52−53. Tanaka, R.; Yano, T.; Nishioka, T.; Nakajo, K.; Breedlove, B. K.; Kimura, K.; Kinoshita, I.; Isobe, K. *Chem. Commun.* **2002**, 1686−1687. Kelly, T. R.; Lebedev, R. *J. Org. Chem.* **2002**, *67*, 2197−2205. Vedernikov, A. N.; Huffmann, J. C.; Caulton, K. G. *Inorg. Chem.* **2002**, *41*, 6867−6874. Malkov, A. V.; Bella, M.; Stará, G. I.; Kočovsky', P. *Tetrahedron Lett.* **2001**, *42*, 3045−3048.

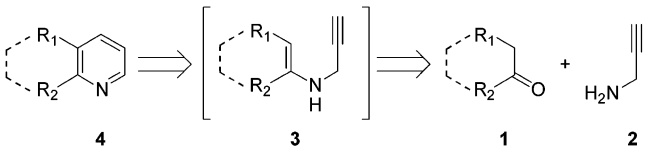
(3) (a) Sutherland, A.; Gallagher, T.; Sharples, C. G. V.; Wonnacott, S. *J. Org. Chem.* **2003**, *68*, 2475−2478. (b) Cosford, N. D. P.; Tehrani, L.; Roppe, J.; Schweiger, E.; Smith, N. D.; Anderson, J.; Bristow, L.; Brodkin, J.; Jiang, X.; McDonald, I.; Rao, S.; Washburn, M.; Varney, M. A. *J. Med. Chem.* **2003**, *46*, 204−206. (c) Enyedy, I. J.; Sakamury, S.; Zaman, W. A.; Johnson, K. M.; Wang, S. *Biorg. Med. Chem. Lett.* **2003**, *13*, 513−517. (d) Burgey, C. S.; Robinson, K. A.; Lyle, T. A.; Sanderson, P. E. J.; Lewis, S. D.; Lucas, B. J.; Krueger, J. A.; Singh, R.; Miller-Stein, C.; White, R. B.; Wong, B.; Lyle, E. A.; Williams, P. D.; Coburn, C. A.; Dorsey, B. D.; Barrow, J. C.; Stranieri, M. T.; Holahan, M. A.; Sitko, G. R.; Cook, J. J.; McMasters, D. R.; McDonough, C. M.; Sanders, W. M., Wallace, A. A.; Clayton, F. C.; Bohn, D.; Leonard, Y. M.; Detwiler, T. J.; Lynch, J. J.; Yan, Y. M.; Chen, Z. G.; Kuo, L.; Gardell, S. J.; Shafer, J. A.; Vacca, J. P. *J. Med. Chem.* **2003**, *46*, 461−463. (e) Narendar, P.; Parthiban, J.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. *Biol. Pharm. Bull.* **2003**, *26*, 182−187. (f) Ravlee, I.; Sivakumar, R.; Muruganantham, N.; Anbalagan, N.; Gunasekaran, V.; Leonard, J. T. *Chem. Pharm. Bull.* **2003**, *51*, 162−170. (g) Faul, M. M.; Ratz, A. M.; Sullivan, K. A.; Trankle, W. G.; Winnerroski, L. L. *J. Org. Chem.* **2001,** *66*, 5772−5782. Bouras, A.; Boggetto, N.; Benatalah, Z.; de Rosny, E.; Sicsic, S.; Reboud-Ravaux, M. *J. Med. Chem.* **1999**, *42*, 957−962. (h) Phillips, G.; Davey, D. D.; Eagen, K. A.; Koovakkat, S. K.; Liang, A.; Ng, H. P.; Pinkerton, M.; Trinh, L.; Whiltow, M.; Beatty, A. M.; Morrissey, M. M. *J. Med. Chem.* **1999**, *42*, 1749−1756.

(4) For reviews, see: Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581−590; Daly, J. W.; Pinder, A. R. *Nat. Proc. Rep.* **1992**, *9*, 491−504. Spande, T. F. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 31.

(5) Ciufolini, M. A. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI Press Inc.: London, 1996; Vol. 3, pp 1−55.

10.1021/jo0347260 CCC: $25.00
Published on Web 08/02/2003

SCHEME 1. Retrosynthetic Approach to the Pyridine Scaffold



R_1 = H, alkyl, aryl
R_2 = H, alkyl, aryl, heteroaryl

involved, or the poor yields. More selective methods including one-pot approaches,[9] radical reactions,[10] cycloaddition,[11] and microwave-assisted procedures have been developed.[12] Nevertheless, the development of a straightforward one-pot approach to functionalized pyridines is still a synthetic challenge. We have developed a novel one-pot procedure for the synthesis of pyridines from commercially available ketones (or aldehydes) **1** and propargylamine **2**. From all possible retrosynthetic schemes of six-membered heterocycles, the best of them require one C−C bond and one C-heteroatom disconnection. It was plausible to suppose that condensation reaction of **2** with carbonyl derivatives could give the title targets if after the formation of a C−N linkage giving *N*-propargylenamine derivatives **3** the required C−C bond could be formed by a sequential regioselective 6-*endo*-*dig* annulation/aromatization reaction (Scheme 1).

The endo mode of annulation remains relatively unexplored compared to the exo cyclizations.[13] A variety of methods of selective *endo*-5-*dig* cyclization of 5-en-1-ynes have been developed, but selective 6-*endo*-*dig* cyclizations are scarcely known.[14] We have found that reaction of carbonyl compounds with **2** gives rise to pyridines **4** through sequential amination/6-*endo*-*dig* annulation/aromatization reaction. Herein, we describe the scope and limitations of this new entry to functionalized pyridines.

Results and Discussion

We selected 1,3-diphenyl acetone **1a** for initial studies. Reaction of **1a** with an excess of **2** (**1a**/**2** = 1:2) in ethanol at reflux for 12 h led to the isolation of 2-benzyl-3-phenylpyridine **4a** as the sole reaction product, but only in 32% yield (**1a** was recovered in 64% yield). Carbonyl compounds are known to undergo condensation reaction with primary amines to produce imines. Imines with α-hydrogens would be expected to be capable of imine−enamine isomerization. Such an isomerization has been shown in many cases in reactions involving the α-hydrogen atom of imines.[15] Then the formation of **4a** can occur through annulation/aromatization reaction of the *N*-propargylenamine derivative (R^1 = Ph; R^2 = $PhCH_2$−) generated in situ from the condensation of **1a** and **2**. Usually, aliphatic ketones react slowly with amines and aromatic ketones react even slower than aliphatic ones. Fair yields of amination derivatives can be obtained by the use of high temperature, long reaction time, acidic catalysts, and water removal. We have developed efficient protocols for condensation reactions of 1,3-dicarbonyl derivatives with amines.[16] In particular, gold salts permitted the synthesis of *β*-enaminones from 1,3-dicarbonyl compounds and ammonia/amines at rt providing a milder alternative to previous methodologies. Kobayashi et al.[17] reported that several transition-metal salts exhibit higher catalytic activity compared to conventional Lewis acids in aza-Michael reactions of enones. So we first studied the catalytic activity of various transition-metal salts (mostly chlorides) in the reaction of **1a** and **2** (Table 1).

According to our previous results, gold(III) catalysts were very effective.[16] From all the catalysts screened, $NaAuCl_4 \cdot 2H_2O$ was the most efficient (Table 1, entry 1) for the preparation of **4a** (98% yield). Copper salts were also effective catalysts (Table 1, entries 5−10). Ir(I) and Rh(I) complexes[18] are known to catalyze the addition of amines to acrylic acid derivatives, but in our case these complexes were not active (Table 1, entries 21 and 22). $ZnCl_2$, $AlCl_3$, $TiCl_4$, and other Lewis acids[19] have been reported to be efficient catalysts and water scavengers in the condensation of ketones with amines, but in our hands they showed low activity (Table 1, entries 11 and 20).

We next investigated the reactions of various ketones with **2** in ethanol by using the most effective catalysts found for **4a** and studied the best reactions conditions that could be used with a wide variety of carbonyl derivatives **1b**−**t** by varying the **1**/**2** molar ratio and the reaction temperature for both catalysts. The results are shown in Table 2.

Copper salts were as effective as gold salts when the most reactive ketones were used. In some cases, a slight excess of **2** (**2**/**1** = 1.5) gave satisfactory results, but in

(6) Sutherland, A.; Gallagher, T. *J. Org. Chem.* **2003**, *68*, 3352−3355. Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A. L.; Hogg, R. D.; Kane, P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. A. B.; Warne, M. R. *Tetrahedron Lett.* **2003**, *44*, 1627−1629.

(7) Turner, S. C.; Zhai, H.; Rapoport, H. *J. Org. Chem.* **2000**, *65*, 861−870.

(8) Schmidt, G.; Stoltefuss, J.; Lögers, M.; Brandes, A.; Schmeck, C.; Bremm, K.-D.; Bischoff, H.; Schmidt, D. Ger. Offen. 1999, 42, DE 19741399. Stoltefuss, J.; Lögers, M.; Schmidt, G.; Brandes, A.; Schmeck, C.; Bremm, K.-D.; Bischoff, H.; Schmidt, D. PCT Int. Appl. 1999, 107, WO 9914215. Smith, H. W. Eur. Pat. Appl. 1985, 35, EP 161867.

(9) Bagley, M. C.; Dale, J. W.; Ohnesorge, M.; Xiong, X.; Bower, J. *J. Combinat. Chem.* **2003**, *5*, 41−44. Yehia, N. A. M.; Polborn, K.; Müller, T. J. J. *Tetrahedron Lett.* **2002**, *43*, 6907−6910. Bagley, M. C.; Dale, J. W.; Bower, *Chem. Commun.* **2002**, 1682−1683. Veronese, A. C.; Morelli, C. F.; Basato, M. *Tetrahedron* **2002**, *58*, 9709−9712.

(10) Baker, S. R.; Cases, M.; Keenan, M.; Lewis, R. A.; Tan, P. *Tetrahedron Lett.* **2003**, *44*, 2995−2999. Navarro-Vázquez, A.; García, A.; Domínguez, D. *J. Org. Chem.* **2002**, *67*, 3213−3220.

(11) Coffey, S. C.; Kolis, S. P. May S. A. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T. L., Eds.; Pergamon: Amsterdam, 2002; Vol. 14, pp 257−259 and references therein.

(12) Bagley, M. C.; Lunn, R.; Xiong, X. *Tetrahedron Lett.* **2002**, *43*, 8331−8334. Cherng, Y.-J. *Tetrahedron* **2002**, *58*, 4931−4935.

(13) For recent examples of 5-*endo*-*dig* cyclization of 5-en-1-ynes, see: Iwasawa, N.; Miura, T., Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463−4466 and references therein. For recent examples of 5-exo-dig cyclization of 5-en-ynes, see: Rossi, E.; Arcadi, A.; Abbiati, G.; Attanasi, O. A.; De Crescentini, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1400−1402.

(14) Pastine, S. J.; Youn, S. W.; Sames, D. *Org. Lett.* **2003**, *5*, 1055−1058. Berg-Nielsen, K.; Skatebøl, L. *Acta Chem. Scand. B: Org. Chem. Biochem.* **1978**, *32*, 553−556.

(15) Parcell, R. F.; Hauck, F. P., Jr. *J. Org. Chem.* **1963**, *28*, 3468−3473.

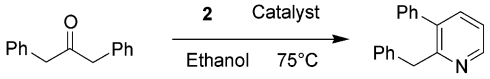
(16) Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F. *Green Chem.* **2003**, *5*, 64−67.

(17) Kobayashi, S.; Kakumoto, K.; Sugiura, M. *Org. Lett.* **2002**, *4*, 1319−1322.

(18) Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960−1964

(19) Borg, G.; Cogan, D. A.; Elmann, J. A. *Tetrahedron Lett.* **1999**, *40*, 6709−6712. Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570−1572. Moretti, I.; Torre, G. *Synthesis* **1970**, 141. Billman, J. H.; Tai, K. M. *J. Org. Chem.* **1958**, *23*, 535−539.

TABLE 1. Effect of Catalyst Choice on Reaction[a] of 1,3-Diphenylacetone 1a with Propargylamine 2



1a **4a**

entry	catalyst	yield[b] (%)	entry	catalyst	yield[b] (%)
1	$NaAuCl_4 \cdot 2H_2O$[c]	98	12	$Cu(NO_3)_2 \cdot 3H_2O$	82 (9)[d]
2	$NaAuCl_4 \cdot 2H_2O$	56[e]	13	$NaPdCl_4$	40 (54)[d]
3	$KAuCl_4$	85 (13)[d]	14	$PtCl_4$	53 (43)[d]
4	AuCl	51 (46)[d]	15	K_2PtCl_4	43 (53)[d]
5	CuI	62 (31)[d]	16	$NiCl_2 \cdot 2H_2O$	37 (63)[d]
6	CuCl	79	17	$AgNO_3$	52 (45)[d]
7	$CuSO_4 \cdot 5H_2O$	62 (37)[d]	18	$Ru^{(III)}Cl_3$	44 (51)[d]
8	$CuCl_2 \cdot 2H_2O$[c]	95	19	$FeCl_3 \cdot 6H_2O$	65 (22)[d]
9	$Cu(OAc)_2$	80 (7)[d]	20	$ZnCl_2$	35 (61)[d]
10	$Cu(CF_3SO_3)_2$	74 (16)[d]	21	$[IrCl(C_8H_{12})]_2$	21 (77)[d]
11	$TiCl_4$	6 (92)[f]	22	$Rh(C_2H_4)(C_5H_7O_2)$	19 (78)

[a] All reactions were carried out with 1 equiv of **1a**, 2 equiv of **2**, and 0.025 equiv of the catalyst in ethanol at reflux for 12 h. [b] GC yield. [c] Reaction time 5 h. [d] Figures in parentheses refer to recovered yield of **1a**. [e] **1a**/**2** = 1:1.5. [f] The reaction was carried out with 1 equiv of **1a**, 2 equiv of **2**, and 0.5 equiv of the $TiCl_4$ in toluene (2 mL) at rt for 5 h and at reflux for 19 h.

other cases the best results were obtained when we used 2.0 or 3.0 equiv of **2**. Increasing the reaction temperature usually resulted an increase of the yield of the pyridine derivative (i.e., **4c** was isolated in 46% yield at 40 °C and 69% yield at 78 °C; Table 2, entries 3 and4). With the less reactive aryl alkyl ketones, a temperature of 100 °C was required (i.e., **4m** was isolated in 50% yield at 78 °C and 65% yield at 100 °C; Table 2, entries 17 and 18). By this method, a series of mono- and polyannelated pyridines in which a five-, six-, seven-, or eight-membered ring is fused at the 2,3-position of the pyridine ring were prepared. The new analogue of the nicotinic acetylcholine receptor agonist[7] **4d** was prepared from tropinone **1d** (Table 2, entry 5). In contrast to our method, the traditional preparation of annelated pyridines through the Friedländer condensation[20] of cyclic ketones with *β*-aminoacrolein provided 2,3-fused pyridines in very poor yields (i.e., 2,3-trimethylenepyridine **4e** was obtained in 16% yield), and the alternative traditional procedures involving thermal rearrangements of *O*-allyl ethers of ketoxymes[21] or intramolecular Diels−Alder reactions of 2-(alkynyl)pyrimidines[22] required heating at temperatures over 200 °C. Steroids bearing fused heterocyclic rings[23] are interesting as modulators of androgen biosynthesis[24] and pituitary gonadotropin inhibitors. Our new approach permitted the synthesis of steroidal derivatives with fused pyridine rings.[25] The gold-catalyzed condensation of 5-androsten-3*β*-ol-17-one **1h** with **2** at 100 °C gave the 5-androsten[17,16-*b*]pyridin-3*β*-ol derivative **4h** in 56% yield. Linear or angular cholestanopyridine derivatives **4i**,**j** were obtained, respectively, by the gold-catalyzed condensation of the 5α-cholestan-3-one **1i** or the 4-cholesten-3-one **1j** with **2**. Different angular polycyclic pyridines were obtained from 3-keto-Δ^4-polycyclic derivatives. Selectivity of the reaction of polycyclic dicarbonyls **1k**,**l** and propargylamine **2** has also been investigated. The reported procedures[25] for androstanopyridine derivatives involved several steps, two of which occurred at temperatures over 200 °C. The linear cholestanopyridine **4i** was previously synthesized[26] through a three-step pyridoannelation of the 5α-cholestan-3-one **1i** by regiospecific alkylation of its *N*,*N*-dimethylhydrazones with bromoethyl-1,3-dioxolane. The angular polycyclic pyridines **4j**,**l** have not been previously reported. According to the results obtained in the preparation on enamine derivatives of steroidal carbonyl compounds,[27] polycyclic dicarbonyl derivatives having conjugated carbonyl groups in the C_3-position undergo selective amination in the 3-position. Then, the target angular pyridines **4j**,**l** could derive from the sequential annulation/aromatization reaction of 3,5-dienyl-3-(*N*-propargyl)-amino intermediates **5**. These results suggest that the regioselective pyridine fusion to the cyclic skeleton could be directed by the presence of a saturated or conjugated carbonyl group in the substrate (Scheme 2).

The preparation of 2-aryl(heteroaryl)-substituted pyridines (Table 2, entries 19−23) through the reaction of methyl aryl(heteroaryl) ketones with **2** represents an alternative to the Suzuki cross-coupling procedure.[28] Aliphatic aldehydes give in general polymeric materials in their reactions with amines because the initially formed imines undergo subsequent aldol condensation. Nevertheless, by adding a slight excess (1.2 equiv) of **2** at rt to a stirred solution of aldehydes **1s**,**t**, we observed by GC/MS the quantitative formation of the amination derivative after 1 h; then, the temperature was raised to 120 °C for 12 h and the 3-alkyl-substituted pyridines **4s**,**t** were isolated after usual workup in good yield (Table 2, entries 24 and 26). In the presence of the gold catalyst (Table 2, entry 25), the pyridine **4s** was obtained in milder conditions and in higher yield. A plausible mech-

(20) Thummel, R. P.; Kohli, D. K. *J. Org. Chem.* **1977**, *42*, 2742−2747.
(21) Kusumi, T.; Yoneda, K.; Kakisawa, H. *Synthesis* **1979**, 221−223.
(22) Frissen, A. E.; Marcelis, A. T. M.; Geurtsen, G.; de Bie, D. A.; van der Plas, H. C. *Tetrahedron* **1989**, *45*, 5151−5162.
(23) Arcadi, A.; Rossi, E. *Synlett* **1997**, 667−668.
(24) Zhang, X.; Sui, Z. *Tetrahedron Lett.* **2003**, *44*, 3071−3073.
(25) Miller, T. C. *J. Heterocycl. Chem.* **1966**, *3*, 338−342. Sterling Drug Inc. U.S. Patent 3409609; *Chem. Abstr.* **1969**, *70*, 47710s.
(26) Chelucci, G.; Gladiali, S. *J. Heterocycl. Chem.* **1988**, *25*, 1761−1765.
(27) Heyl, F. W.; Herr, M. E. *J. Am. Chem. Soc.* **1953**, *75*, 1918−1920.
(28) Feuerstein, M.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 5659−5662.

TABLE 2. Synthesis of Pyridines[a] 4 from the Reaction of Carbonyls with Propargylamine 2

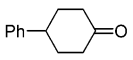
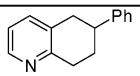
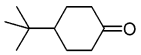
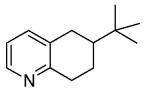
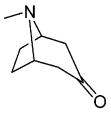
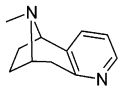
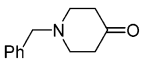
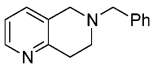
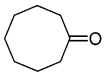
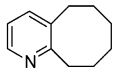
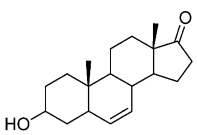
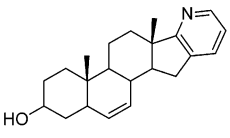
entry	Ketones **1**	Pyridines **4**	Catalyst (T °C)	Time/ h	Yield (%)[b]
1	 **1b**	 **4b**	$NaAuCl_4 \cdot 2H_2O$ (78)	5	74
2	**1b**	**4b**	- (78)	5	15
3	 **1c**	 **4c**	$NaAuCl_4 \cdot 2H_2O$ (78)	5	69
4	**1c**	**4c**	$NaAuCl_4 \cdot 2H_2O$ (40)	6	46
5	 **1d**	 **4d**	$NaAuCl_4 \cdot 2H_2O$ (100)	7	66[c]
6	**1d**	**4d**	$CuCl_2 \cdot 2H_2O$ (100)	7	43[c]
7	 **1e**	 **4e**	$NaAuCl_4 \cdot 2H_2O$ (78)	7	57
8	**1e**	**4e**	$CuCl_2 \cdot 2H_2O$ (78)	7	26[d]
9	 **1f**	 **4f**	$NaAuCl_4 \cdot 2H_2O$ (78)	7	77
10	 **1g**	 **4g**	$NaAuCl_4 \cdot 2H_2O$ (78)	12	67
11	 **1h**	 **4h**	$NaAuCl_4 \cdot 2H_2O$ (78)	12	22

TABLE 2 (Continued)

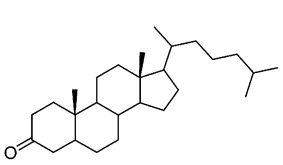
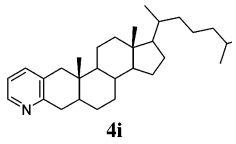
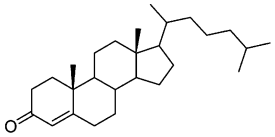
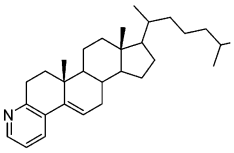
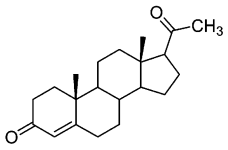
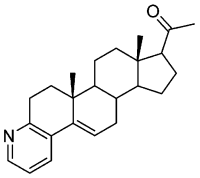
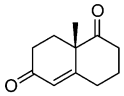
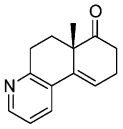
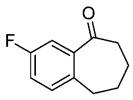
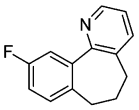
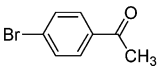
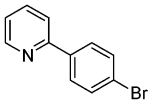
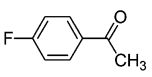
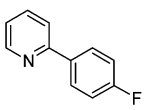
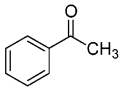
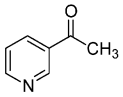
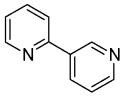
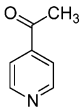
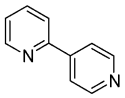
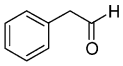
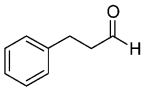
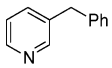
entry	Ketones **1**	Pyridines **4**	Catalyst (T °C)	Time/ h	Yield (%)[b]
12	**1h**	**4h**	(100)	24	56
13	 **1i**	 **4i**	$NaAuCl_4 \cdot 2H_2O$ (100)	24	56[d]
14	 **1j**	 **4j**	$NaAuCl_4 \cdot 2H_2O$ (78)	24	60[d]
15	 **1k**	 **4k**	$NaAuCl_4 \cdot 2H_2O$ (78)	24	64[d]
16	 **1l**	 **4l**	$NaAuCl_4 \cdot 2H_2O$ (78)	24	68
17	 **1m**	 **4m**	$NaAuCl_4 \cdot 2H_2O$ (78)	12	50
18	**1m**	**4m**	$NaAuCl_4 \cdot 2H_2O$ (100)	6	65
19	 **1n**	 **4n**	$NaAuCl_4 \cdot 2H_2O$ (100)	12	68
20	 **1o**	 **4o**	$NaAuCl_4 \cdot 2H_2O$ (100)	12	66

TABLE 2 (Continued)

entry	Ketones **1**	Pyridines **4**	Catalyst (T °C)	Time/ h	Yield (%)[b]
21	 **1p**	 **4p**	$NaAuCl_4 \cdot 2H_2O$ (100)	12	78[d]
22	 **1q**	 **4q**	$CuCl_2 \cdot 2H_2O$ (120)	24	85[d]
23	 **1r**	 **4r**	$CuCl_2 \cdot 2H_2O$ (100)	24	60[d]
24	 **1s**	 **4s**	- (120)	12	88[e]
25	**1s**	**4s**	$NaAuCl_4 \cdot 2H_2O$ (78)	12	96
26	 **1t**	 **4t**	- (120)	24	70[e]

[a] Unless otherwise stated, reactions were carried out in ethanol (2 mL) using 1 equiv of **1**, 1.5 equiv of **2,** and 0.025 equiv of catalyst. [b] Yields are given for isolated products. [c] 3.0 equiv of **2** was used. [d] 2.0 equiv of **2** was used. [e] To a solution of 1 equiv of **1** in ethanol (2 mL) was added 1.2 equiv of **2**, and the mixture was stirred for 1 h at rt. Then, the mixture was heated at 120 °C for 24 h.

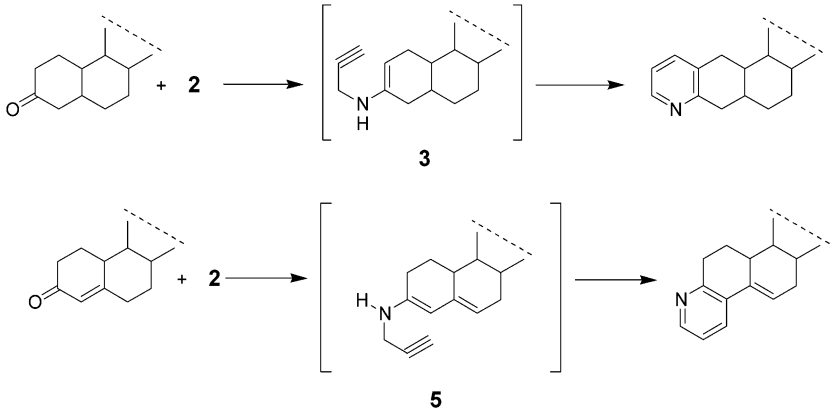
anism consists of (1) formation of the imino intermediate **6** through the metal salt catalyzed condensation reaction of the ketone **1** with **2**, (2) imine−enamine isomerization to give **7**, (3) regioselective 6-*endo-dig* intramolecular nucleophilic attack of the carbon of the enamino moiety to the activated carbon−carbon triple bond to give an organometallic intermediate **8**, (5) protonolysis of the C_{sp2}−M bond to give the dehydropyridine **9**, and (6) dehydrogenation reaction to afford the pyridine derivative **4** (Scheme 3). An effective catalyst of this sequential amination/cyclization reaction should act simultaneously as a Lewis acid and as a transition metal.[29] MX_n should catalyze the nucleophilic attack of the amino group of **2** to the carbonyl carbon through the formation of a complex with the C=O group. MX_n should act as transition-metal catalyst by forming a complex with the alkyne groups that facilitates the nucleophilic attack of the enamine to the electron-deficient carbon. In previous studies, we observed the high efficiency of gold(III) catalysis as Lewis acid in the condensation reaction of *o*-amino aromatic carbonyl compounds with ketones containing active methylene groups[30] and both as Lewis acid/transition metal[31] in sequential amination/annulation reactions of α-propargyl dicarbonyls with amines, amino alcohols and

(29) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764−765.

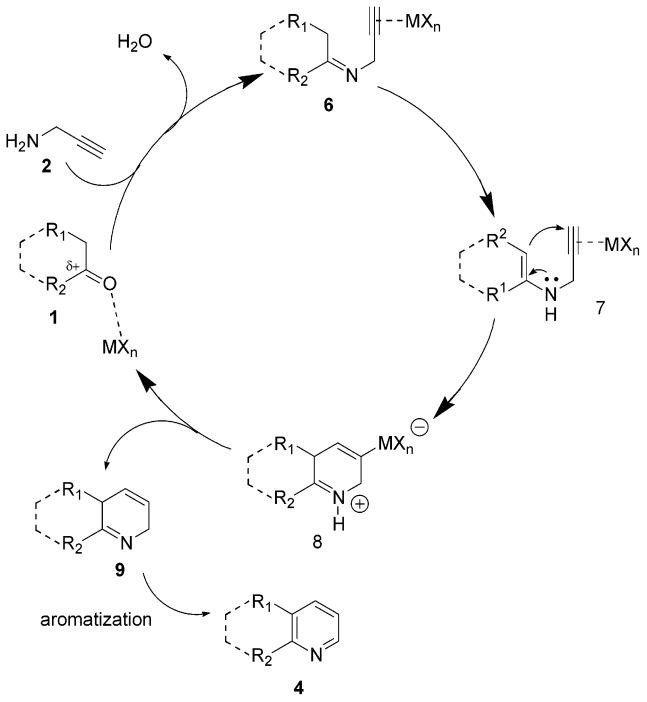
(30) Arcadi, A.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Synlett* **2003**, 203−206.

(31) Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Tetrahedron: Asymmetry* **2001**, *12*, 2715−2720. Arcadi, A.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *Adv. Synth. Catal.* **2001**, *343*, 443−446.

SCHEME 2. Linear vs Angular Polycyclic Pyridines



SCHEME 3. Transition-Metal-Catalyzed Sequential Amination/Cyclization/Aromatization Reaction: Proposed Mechanism



α-aminoesters. The acetylenic bond has been proved to have a regio-/chemoselective interaction with copper salts.[32]

Conclusions

The condensation reaction of carbonyl compounds with propargylamine represents a new general one-pot entry into fuctionalized pyridines. The formation of the pyridines is suggested to proceed through the sequential amination of carbonyl compounds followed by regioselective 6-*endo*-*dig* cyclization of the *N*-propargylenamine (*N*-propargyldienamine) intermediate and aromatization reaction. The reaction requires a catalyst. Gold(III) salts are the most efficient and selective catalysts and their application is general, but copper salts are also efficient catalysts when reactive ketones are used. The gold-catalyzed condensation reaction of cyclic ketones led to fused pyridines in which a five-, six-, seven-, or eight-membered ring is fused at the 2,3-position of the pyridine ring. This new synthetic approach was successfully extended to the synthesis of steroidal derivatives with fused pyridine rings and polyannelated pyridines. Whereas linear polycyclic pyridines are regioselectively obtained by the gold-catalyzed condensation reaction of polycyclic carbonyl compound, the angular polycyclic pyridines are obtained starting from the corresponding α,*β*-unsaturated derivatives. Selective amination of the unsaturated carbonyl groups was observed in polycyclic dicarbonyl compounds.

Experimental Section

General Experimental Procedure for the Sequential Amination/Annulation/Aromatization Reactions of Ketones 1 with Propargylamine 2. To a 50 mL stainless steel autoclave charged with a solution of the ketone **1** (1.26 mmol) in absolute ethanol (5 mL) were added propargylamine 2 (2.52 mmol) and the catalyst (0.03 mmol). The resulting mixture was heated at reflux under stirring or at 100 or 140 °C.The reaction was monitored by TLC and GC−MS. After cooling, the mixture was filtered to remove the catalyst, and the solvent was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, *n*-hexanes−ethyl acetate mixtures) to give pyridine **4**. Alternatively, the residue was dissolved in ethyl acetate and extracted three times with a 6 M solution of aqueous hydrochloric acid. The combined aqueous extracts were washed with ethyl acetate, solid NaOH was added until pH = 8, and the mixture was extracted three times with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The desired product was distilled under vacuum.

The following products were identified by comparison of their physical and spectral data with those given in the cited references: 2-benzyl-3-phenylpyridine[15] **4a**, 6-*tert*-butyl-5,6,7,8-tetrahydroquinoline[33] **4c**, 6-benzyl-5,6,7,8-tetrahydro[1,6]-naphthyridine[34] **4e**, 6,7-dihydro-*5H*-1-pyrindine **4f** and 5,6,7,8,9,-10-hexahydrocycloocta[*b*]pyridine[22] **4g**, 5α-cholest-2-eno[3,2-*b*]pyridine[26] **4i**, 2-(4-bromophenyl)pyridine **4n** and 2-phenylpyridine[35] **4p**, 2-(4-fluorophenyl)pyridine[36] **4o**, [2,3′]bipyridine

(32) Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. *Tetrahedron Lett.* **2000**, *41*, 9195−9198.

(33) Hönel, M.; Vierhapper, W. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1933−1939.

(34) Shiozawa, A.; Ichikawa, Y.; Komuro, C.; Kurashige, S.; Miyazaki, H. *Chem. Pharm. Bull.* **1984**, *32*, 2522−2529.

(35) Gutierrez, M. A.; Newkome, G. R.; Selbin, J. *J. Organomet. Chem.* **1980**, *202*, 341−350.

(36) Chkurko, O. P.; Baram, S. G.; Mamajeev, V. P. *Khim. Geterotsikl Soedin.* **1983**, *1*, 66−72.

4q and [2,4′]bipyridine[37] **4r**, 3-phenypyridine[28] **4s,** and 3-benzylpyridine[38] **4t**.

Acknowledgment. We gratefully acknowledge the Università degli Studi di L'Aquila and the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR) for financial support.

Supporting Information Available: Experimental information including characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0347260

(37) De Koning, A. J.; Budzelaar, J.; Boersma, J.; Van der Kerk, G. J. M. *J. Organomet. Chem*. **1980**, *199*, 153−169.
(38) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem*. **1985**, *50*, 3232−3234.