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Gold(III)-Mediated Aldol Condensations Provide Efficient Access to Nitrogen Heterocycles

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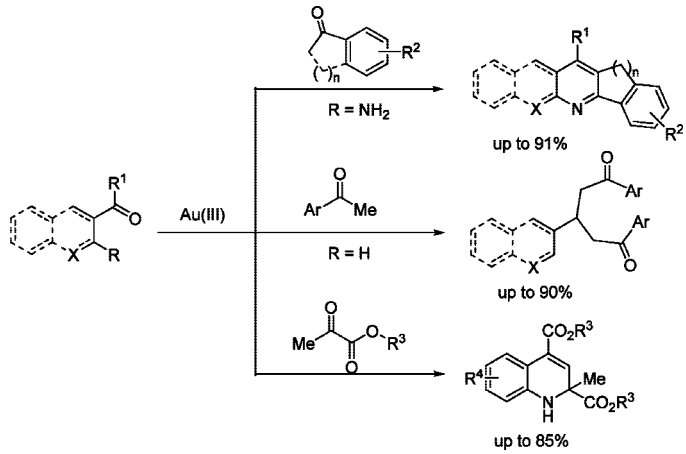
ABSTRACT



Quinolines, dihydroquinolines, and aza-xanthones can be synthesized efficiently and under mild reaction conditions by means of a reaction sequence employing Au(III)-catalyzed aldol reactions as the key step.

Polycyclic N-heterocycles form the basic frameworks of numerous natural product classes and hold a prominent role in pharmaceutical and agrochemical research.[1] In particular, quinolines and their derivatives often are endowed with biological activity including compounds with antitumor activity,[2] CysLT (LTD4) receptor antagonists[3] and HIV-1 replication inhibitors.[4] For quinoline synthesis, the Friedländer annulation[5] is widely used. It proceeds both in the presence of Brønsted[6] or Lewis acid catalysts[7] and under

(1) (a) *Comprehensive Heterocyclic Chemistry*; Katritzky, A., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, UK, 1996. (b) Martin, S. F. In *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1987; Vol. *30*, pp 251−377. (c) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329–332. (d) Jeffs, P. W. In *The Alkaloids*; Rodrigo, R. G. A., Ed.; Academic: New York, 1981; Vol. 19, pp 1−80.

(2) Atwell, G. J.; Baguley, B. C.; Denny, W. A. *J. Med. Chem.* **1989**, *32*, 393–401.

(3) Selected references: (a) Sawyer, J. S.; Thrasher, K. J.; Bach, N. J.; Stengel, P. W.; Cockerham, S. L.; Silbaugh, S. A.; Roman, C. R.; Froelich, L. L.; Fleisch, J. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 249–252. (b) Zwaagstra, M. E.; Timmerman, H.; van de Stolpe, A. C.; de Kanter, F. J.; Tamura, M.; Wada, Y.; Zhang, M.-Q. *J. Med. Chem.* **1998**, *41*, 1428–1438. (c) Chambers, R. J.; Antognoli, G. W.; Cheng, J. B.; Kuperman, A. V.; Liston, T. C.; Marfat, A.; Owens, B. S.; Pillar, J. S.; Shirley, J. T.; Watson, J. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3577–3582.

(4) Zouhiri, F.; Desmaele, D.; d'Angelo, J.; Ourevitch, M.; Mouscadet, J.-F.; Leh, H.; Le Bret, M. *Tetrahedron Lett.* **2001**, *46*, 8189–8192.

(5) (a) Cheng, C. C.; Yan, S. J. *Org. React.* **1982**, *28*, 37–201. (b) Thummel, R. P. *Synlett* **1992**, 1–12. (c) Rusanov, A. L.; Komarova, L. G.; Prigozhina, M. P.; Likhatchev, D. Y. *Russ. Chem. Rev.* **2005**, *74*, 671–683.

(6) (a) Na, J. E.; Lee, K. Y.; Park, D. Y.; Jae, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 323–326. (b) 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. (c) Jia, C.-S.; Zhang, Z.; Tu, S.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2006**, *4*, 104–110.

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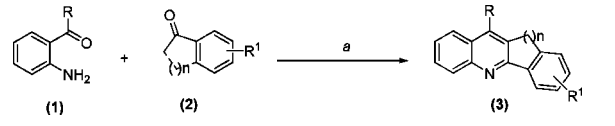
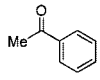
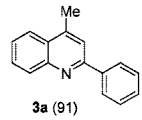
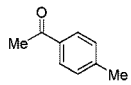
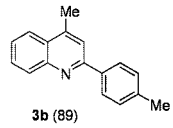
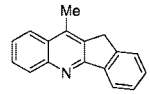
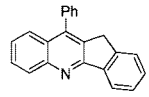
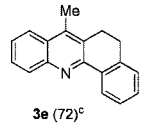
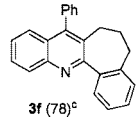
noncatalyzed thermal conditions (heating in the presence of base or heating to temperatures up to 250 °C). In the course of a program aimed at the development of new methodology for the synthesis of heterocycle classes endowed with biological activity[8] we were inspired by a recent report on a gold catalyzed quinoline synthesis[9] to explore the versatility of gold-catalysis[10] for the synthesis of a collection of N-heterocycles. Here, we report our preliminary results on gold catalyzed condensation reactions leading to quinoline, dihydroquinoline, and aza-xanthone frameworks.

Table 1. Synthesis of Quinolines from Aryl Alkyl Ketones

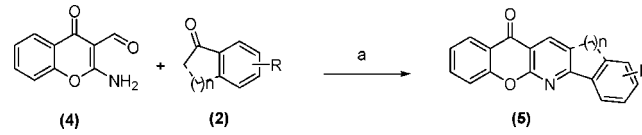


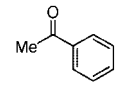
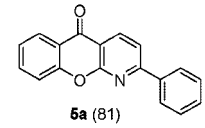
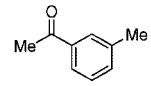
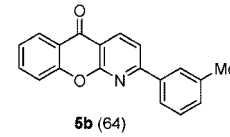
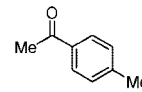
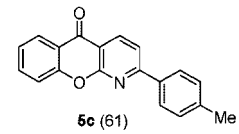
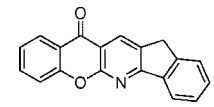
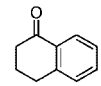
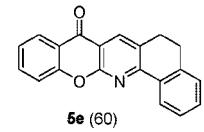
Entry	(1)	(2)	3 (yield %)[b]
1.	 1a	 2a	 3a (91)
2.			 3b (89)
3.			 3c (82)[c]
4.			 3d (67)[c]
5.			 3e (72)[c]
6.			 3f (78)[c]

[a] $AuCl_3$ (5 mol %), $AgSbF_6$ (15 mol %), **2** (1.2 equiv), MeCN/MeOH (4:1), rt, 8 h. [b] Isolated yields. [c] Reaction perforemd at 50 °C, 8 h.

In initial experiments, the Friedländer-type condensation of acetophenone (**2a**) in the reaction with 2-aminoacetophenone (**1a**) leading to quinoline **3a** was investigated. While $AuCl_3$ did catalyze the reaction at room temperature leading to the desired quinoline **3a** in low yield, Au(I) was not catalytically active under a variety of conditions. Elevation of the temperature resulted in an increased yield. However the best results were obtained using $AuCl_3$ and $AgSbF_6$ in a ratio of 1:3 in acetonitrile/methanol (4:1) at room temperature. After 8 h, the reaction was complete and yielded **3a** in 91% yield (Table 1, entry 1). Both cyclic and acyclic acetophenones displayed appreciable reactivity under these reaction conditions yielding quinoline-fused polycycles with preparatively very useful results (Table 1). For cyclic aryl alkyl ketones, warming to 50 °C was required.

Table 2. Synthesis of Azaxanthones from Aryl Alkyl Ketones



Entry	(2)	5 (yield %)[b]
1.		 5a (81)
2.		 5b (64)
3.		 5c (61)
4.		 5d (65)
5.		 5e (60)

[a] $AuCl_3$ (5 mol %), $AgSbF_6$ (15 mol %), **2** (1.2 equiv), MeCN/MeOH (4:1), rt, 8 h [b] isolated yields.

These Au(III)-catalyzed condensations provide a wider scope for the synthesis of *N*-heterocycles than previously reported similar catalytic transformations which mostly employed more reactive 1,3-dicarbonyl compounds,[9] often under harsher reaction conditions (e.g., $NaAuCl_4$, 80−140 °C, 0.5 h to 4 d).[11] In order to generate diverse *N*-heterocyclic systems using gold-catalyzed condensation methodology, we employed 2-amino-3-formylchromone (**4**) with acetophenone

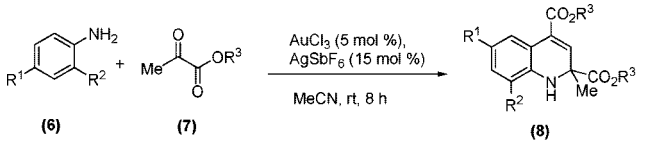
(7) (a) Wang, H.-M.; Kang, I.-J.; Chen, L.-C. *Heterocycles* **2003**, *60*, 1899–1905. (b) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257–4259. (c) Yadav, J. S.; Reddy, B. V. S.; Sreedhar, P.; Rao, R. S.; Nagaiah, K. *Synthesis* **2004**, 2381–2385. (d) Wu, J.; Zhang, L.; Diao, T.-N. *Synlett* **2005**, 2653–2657.

(8) (a) Koch, M. A.; Schuffenhauer, A.; Scheck, M.; Wetzel, S.; Casaulta, M.; Odermatt, A.; Ertl, P.; Waldmann, H. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 17272–17277. (b) Wetzel, S.; Schuffenhauer, A.; Roggo, S.; Ertl, P.; Waldmann, H. *Chimia* **2007**, *61*, 355–360.

using reaction conditions described in Table 1. In the reaction, the desired azaxanthone **5a** was cleanly formed in 81% yield. By analogy, different cyclic aryl alkyl ketones yielded fused azapolycycles in high yields at room temperature (Table 2). Aza-xanthones are of substantial interest due to their pronounced biological activity.[12]

Intriguingly and unexpectedly, the use of α-keto esters (**7**, 2.2 equiv) instead of aryl alkyl ketones in the gold catalyzed condensation with 2-aminoacetophenone (1.0 equiv) and also *p*-anisidine or aniline itself yielded dihydroquinolines **8** (Scheme 1).[13,14] Dihydroquinolines are of significant interest to medicinal chemistry research,[15] and new synthetic routes to them are highly desired.

Scheme 1. Gold-Mediated Synthesis of Dihydroquinolines



(6) (7) (8)

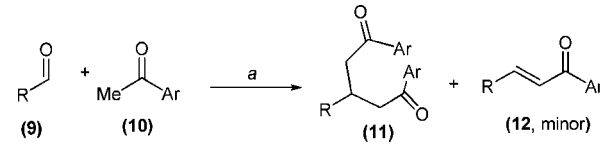
8a; R^1 = H, R^2 = C(O)Me, R^3 = Et, 80%
8b; R^1 = H, R^2 = C(O)Me, R^3 = Me, 85%
8c; R^1 = H, R^2 = C(O)Ph, R^3 = Me, 82%
8d; R^1 = OMe, R^2 = H, R^3 = Et, 56%
8e; R^1 = R^2 = H, R^3 = Et, 51%

These results underscore the synthetic versatility offered by gold catalysis for the synthesis of such polycyclic heterocycles. Thus, under the conditions described, a moderate variation in the structure of the starting materials gives efficient access to a substantially diverse collection of structurally different, biologically relevant *N*-heterocycle classes.

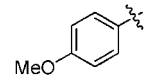
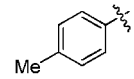
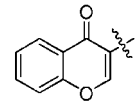
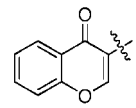
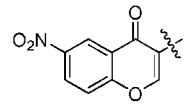
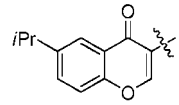
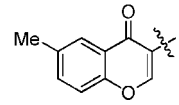
In order to develop a mechanistic rationale for the different transformations described above we assumed that the condensation reactions involve gold-mediated formation of enolates followed by an addition reaction.[16] In order to probe this notion, we investigated the model reaction of benzaldehyde with acetophenone in acetonitrile in the presence of the gold and silver salts under the conditions described above.

Surprisingly the expected α-*β*-unsaturated ketone **12** (R = Ar = Ph) was obtained only as a minor product, and 1,5-diketone **11a** was isolated in 74% yield (Table 3, entry 1). Subsequent experiments revealed that various aromatic aldehydes yielded 1,5-diketones in high yields (Table 3, entries 1−8). However aldehydes with electron-withdrawing substituents (e.g., Cl, Br) and aliphatic aldehydes did not give the analogous products. The reaction of cinnamaldehyde with acetophenone led to formation of a product mixture. When phenylacetylene was employed instead of acetophenone, compound **11a** was obtained in similar yield (70%). Obviously under these reaction conditions phenylacetylene is rapidly hydrated to yield acetophenone which then enters the aldol reaction sequence. This possibility is further supported by the fact that when $Au(PPh_3)Cl$ was used instead of $AuCl_3$ under strictly anhydrous conditions no reaction with the alkyne was detected.

Table 3. Synthesis of 1,5-Diketones from Aldehydes



(9) (10) (11) (12, minor)

Entry	R	Ar	**11** (yield %)[b]
1.		Ph	**11a** (74)
2.		Ph	**11b** (90)
3.		Ph	**11c** (90)
4.		Ph	**11d** (78)
5.		*p*-Tol	**11e** (72)
6.		Ph	**11f** (67)
7.		*p*-Tol	**11g** (74)
8.		Ph	**11h** (72)

[a] $AuCl_3$ (5 mol %), $AgSbF_6$ (15 mol %), **10** (2.2 equiv), MeCN, rt, 8−12 h [b] Isolated yields.

(9) (a) Arcadi, A.; Chiarini, M.; Giuseppe, S. Di; Marinelli, F. *Synlett* **2003**, 203–206. (b) Arcadi, A.; Bianchi, G.; Giuseppe, S. D.; Marinelli, F. *Green Chem.* **2003**, *5*, 64–67.

(10) Reviews: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180–3211. (b) Hoffmann-Rö der, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (c) Sherry, B. D.; Toste, F. D. *Chemtracts Org. Chem.* **2005**, *18*, 14. (d) Ma, S.; Yu, S.; Gu, Z. *Angew. Chem., Int. Ed.* **2006**, *45*, 200. (e) Nieto-Oberhuber, C.; López, S.; Jime'nez-Nu'nez, E.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 5916. (f) Widenhoefer, R.; Han, X. *Eur. J. Org. Chem.* **2006**, 4555. (g) Hashmi, A. S. K.; Hutchings, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7896. (h) Fürstner, A.; Davies, P. W.*Angew. Chem., Int. Ed.* **2007**, *46*, 3410–3449.

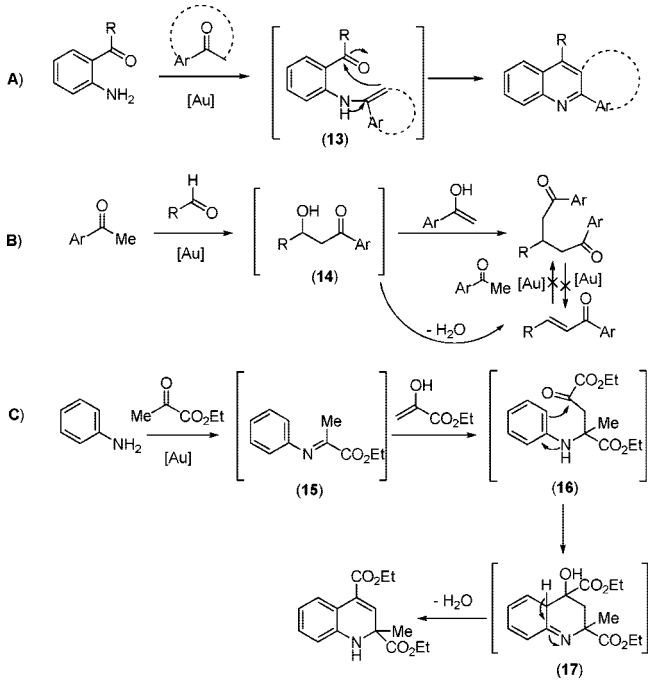
(11) Atechian, S.; Nock, N.; Norcross, R. D.; Ratni, H.; Thomas, A. W.; Verron, J.; Masciadri, R. *Tetrahedron* **2007**, *63*, 2811–2823.

(12) For reports on xanthone and related molecules, see: (a) Peres, V.; Nagem, T. J.; Oliveira, F. F. *Phytochemistry* **2000**, *55*, 683–710. (b) Ciganek, E.; Uyeda, R. T.; Cohen, M.; Smith, D. H. *J. Med. Chem.* **1981**, *24*, 336–341. (c) Recanatini, M.; Bisi, A.; Cavalli, A.; Belluti, F.; Gobbi, S.; Rampa, A.; Valenti, P.; Palzer, M.; Palusczak, A.; Hartmann, R. W. *J. Med. Chem.* **2001**, *44*, 672–680, and references therein.

We propose that the gold catalyst serves as Lewis acid in both formation of ketone enolates and their addition reactions. However, gold catalysis of these particular transformations under the conditions given significantly differs from possible catalysis by other Lewis acids. Thus, the use of $ZnCl_2$, $AlCl_3$ or BF_3•OEt_2 did not lead to formation of 1,5-diketones.

By analogy to this mechanistic proposal, the formation of quinolines detailed above (Scheme 2, **A**) possibly begins with imine formation facilitated by the Lewis acidity of the gold catalyst, followed by enamine addition (**13**) to the ketone. Water elimination eventually leads to quinoline formation. This mechanism is supported by a report of a successful enamine intermediate isolation in a related gold-catalyzed reaction.[9]

Scheme 2. Proposed Mechanisms for the Gold-Catalyzed Condensation Reactions



Similarly, the reaction of aldehydes with acetophenones will involve intermediate **14** which is generated after enolate addition to the aldehyde (Scheme 2, **B**). Attack of a further enolate on **14** leads to 1,5-diketones **11**. Water elimination would yield the minor product **12**. However, in a separate reaction of **12** with acetophenone in the presence of the gold catalyst, formation of **11** was not observed. Also, when **11** was treated under the same reaction conditions but without acetophenone for 48 h, **12** was not formed. These findings suggest that both products probably originate from **14**.

Dihydroquinoline (**8**) formation most likely begins with the generation of an imine from the aniline and the ketoester (Scheme 2, **C**), followed by addition of the enolate to the imine. Keto esters are more reactive substrates than acetophenones and, therefore, should add to the α-imino ester moiety (to give **16**) which is a good electrophile[17] in the presence of a Lewis acid. An electron-rich benzene ring could add to the keto ester group (to give **17**), and water elimination followed by proton shift would eventually form the dihydroquinoline **8**.

In conclusion, we have demonstrated the versatility of gold-catalyzed aldol condensation reactions for the synthesis of several different biologically relevant *N*-heterocycle classes. Efficiency and ease of operation make these transformations highly useful for the synthesis of compound collections for chemical biology and medicinal chemistry research.

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

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