Gold-Catalyzed Synthesis of Tetrazoles from Alkynes by C–C Bond Cleavage**

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Cycloadditions of azides with alkynes to form triazoles under thermal conditions (Huisgen cycloaddition) or in the presence of copper [click reaction, copper-catalyzed azide–alkyne cycloaddition (CuAAC)] are reactions of fundamental importance in organic chemistry. Triazoles can also be obtained by means of ruthenium, silver, and iridium catalysis, as well as by a zinc-mediated process. In sharp contrast, very different reactivity has been observed in the reaction of terminal alkynes with TMSN$_3$ in the presence of group 11 metal salts and complexes. Thus, the group of Jiao recently made the remarkable observation that alkynes (1; $R =$ alkyl, aryl, alkenyl) react with TMSN$_3$ in the presence of Ag$_2$CO$_3$ as catalyst to form nitriles (2; Scheme 1).

The formation of nitriles (2) and carboxamides (3) from alkynes (1) by aryl–alkyne C(sp$^2$)/C$_0$/C(sp) bond cleavage with the concomitant insertion of four nitrogen atoms (Scheme 3) was reported using [Au(PPh$_3$)Cl] and AgCO$_3$ in the presence of H$_2$O and trifluoroacetic acid (TFA) to form carboxamides.

The formation of nitriles (2) and carboxamides (3) was proposed to proceed by nucleophilic addition of azide to (h$_2$-alkyne)metal complexes to form the intermediates 4a, 4b, with subsequent protonolysis to give the alkenyl azides 5 (Scheme 2). The nitriles 2 could then be produced by a 1,3-dipolar cycloaddition and subsequent fragmentation of 6. In the presence of TFA, protonation of 5 would form 7, which could evolve by a Schmidt rearrangement to give the amides 3. A somewhat related cleavage of triple bonds to form nitriles has been reported using TMSN$_3$ and N-iodosuccinimide, and was proposed to proceed via 2-iodo-2H-azirines.

We now report that by using the JohnPhos/gold(I) catalyst A, which allows performing reactions in the absence of Ag$_3$, the N-aryl tetrazoles 8 are obtained from 1 by C–C bond cleavage with the concomitant insertion of four nitrogen atoms (Scheme 3). In this transformation gold plays a dual role, first activating the alkyne towards nucleophilic attack and then generating the Brønsted acid required for the transformation of the alkenyl azide into the final tetrazole.

We first studied the reaction of the aryl alkynes 1a–e with TMSN$_3$ and complex A under stoichiometric conditions.

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Surprisingly, the reaction gave 5-methyl-1-aryl-1H-tetrazole–gold(I) complexes (9a–c) as crystalline white solids, whose structures were determined by X-ray diffraction (Scheme 4).[17,18] The complex 9a was also obtained in 56% yield by reaction of neutral [(JohnPhos)AuCl] with phenyl acetylene (1a) and TMSN₃ in the presence of AgSbF₆.

We have provided evidence that the rate-determining step in certain catalytic reactions involving alkynes is the ligand substitution reaction between the complexes [Au–(product)L]⁺ and the starting alkyne.[19] The isolation of stable gold(I) complexes (9a–c) under stoichiometric conditions shows that in this case the development of a catalytic process for the synthesis of tetrazoles would be a challenging task, since this ligand substitution would be particularly slow. Thus, either no reaction or very poor yields of the tetrazole 8d were obtained with complex A in MeCN, CH₂Cl₂, or toluene (Table 1, entries 1–4). Better results were obtained in 1,2-dichloroethane at 80 °C (Table 1, entries 5 and 6). In contrast, the related gold(I) catalysts B and C, and complexes D–G with NHC (N-heterocyclic carbene), phosphite, or less-bulky phosphine ligands led to poor results (Table 1, entries 9 and 16).

A further improvement was achieved by performing the reaction in the presence of iPrOH (Table 1, entry 7). Under these reaction conditions, aryl-, heteroaryl-, and alkyl-substituted alkynes react with TMSN₃ to give the corresponding tetrazoles 8 (Scheme 5). Lower yields of the tetrazoles 8g and 8k were obtained from employing aryl alkynes substituted with electron-withdrawing groups. In the case of p-nitrophenylacetylene (1c), no tetrazole was formed and the alkynyl azide 5c was isolated instead (23% yield). Diphenyl acetylene, having an internal alkyne, failed to give the corresponding tetrazole. Aliphatic alkynes also reacted to give tetrazoles (8m–o). Interestingly, whereas cyclohexylacetylene provided 8m in good yield as the sole product, 1-pentyne gave 8n along with 1-methyl-5-propyl-1H-tetrazole (8n’, 10:1 ratio) and cyclopropylacetylene gave 8o and 8o’ (1:3 ratio).

All these results can be accommodated by a mechanism proceeding by reaction between a (n-alkyne)gold(I) complex and HN₃, formed in situ from TMSN₃ and iPrOH, to give 4b, which undergoes protodeauration to give 5 (Scheme 6), and is in agreement with that proposed for the formation of nitriles and carbonodimides.[9,10] Protonation of 5 would give the iminodiazonium cation 7, which could evolve to form the nitrilium cation 10 by migration of R group (path a). Competitive migration of the methyl group (path b) explains the formation of regioisomers 8m and 8o’ in the reactions of 1-pentyne and cyclopropylacetylene. It is interesting that preferential migration of the methyl group has been observed in the Schmidt reaction of methyl cyclopropyl ketone in aqueous sulfuric acid at lower acid strengths.[12a] Finally, a formal 1,3-dipolar cycloaddition of HN₃ to 10 would lead to 8.[20,21] It is important to note that nitrimium cations 10 have been reported to give also triazolium salts by reaction of the

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**Table 1:** Catalyst and solvent optimization for the formation of 8b.

| Entry | [Au] | Solvent | T [°C] | Yield [%] |
|-------|------|---------|--------|----------|
| 1     | A    | MeCN    | 23     |         |
| 2     | A    | MeCN    | 80     | 8        |
| 3     | A    | CH₂Cl₂  | 40     |         |
| 4     | A    | toluene | 110    | 9        |
| 5     | A    | DCE     | 80     | 40       |
| 6     | A    | DCE     | 80     | 59       |
| 7     | A    | DCE     | 80     | 78–81    |
| 8     | A    | DCE     | 110    | 38       |
| 9     | B    | DCE     | 80     | 8        |
| 10    | C    | DCE     | 80     | 7        |
| 11    | D    | DCE     | 80     |         |
| 12    | D’   | DCE     | 80     |         |
| 13    | E    | DCE     | 80     |         |
| 14    | F    | DCE     | 80     | 15       |
| 15    | G    | DCE     | 80     | 18       |
| 16    | [Au(PPh₃)Cl]/Ag₂CO₃ | DCE | 80 |         | 80 |

[a] Determined by NMR spectroscopy. [b] No reaction. [c] 10 mol% catalyst. [d] iPrOH (4–10 equiv).

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**Scheme 4.** Formation of the tetrazole–gold(I) complexes 9a–c and their X-ray crystal structures. For the ORTEP plots the thermal ellipsoids are shown at 50%. Au yellow, F green, N blue, O red, P violet, Sb light blue.
initial azide addition product with a second nitrilium cation, a process that was not observed under these reaction conditions. Although formation of digold(I) intermediates (11) by reaction of 4b with a second equivalent of a gold(I) complex cannot be entirely excluded, the following experiments using (1-azidovinyl)benzene (5a, R = Ph) as the substrate strongly suggest that the transformation of 4b into 7 is a Brønsted acid catalyzed reaction: 1) reaction of 5a with TMSN₃ and iPrOH with A under the standard reaction conditions gave 8a (42% yield by NMR); 2) in the absence of iPrOH, 5a gave 8a in only 12% yield; 3) only traces of 8a were obtained in the absence of gold catalyst A; 4) replacing iPrOH and A by HOAc (2 equiv) led to 8a in 78% yield. Presumably, under the gold(I)-catalyzed conditions, the reaction of 1a, TMSN₃, and complex A was carried out in CH₂Cl₂ containing 1.1 equivalents of D₂O, the deuterated complex [D₂]-9a was obtained.

Tetrazoles, which are important in medicinal chemistry and as energetic materials, have been obtained by 1,3-dipolar cycloaddition of azides with activated nitriles and by cycloaddition of hydrazoic acid with the Ugi adducts generated in situ from carbonyl compounds, amines, and isonitriles. This new reaction demonstrates that this new class of heterocyclic compounds can be prepared under relatively mild reaction conditions from readily available alkynes in a process in which gold(I) catalyzes the formation of alkenyl azides by nucleophilic attack onto the alkynes, as has been shown in the formation of carboxamides. In addition, gold presumably provides the Brønsted acid required for the protodeauration and final formation of tetrazoles from the intermediate alkenyl azides under anhydrous, catalytic conditions. Further work aimed at developing new catalysts for the synthesis of tetrazoles from alkynes is in progress.

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[1] a) R. Huisgen, Proc. Chem. Soc. 1961, 357–396; b) R. Huisgen, Angew. Chem. 1963, 75, 604–637; Angew. Chem. Int. Ed. Engl. 1963, 2, 565–598.
[2] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, Angew. Chem. 2001, 113, 2056–2075; Angew. Chem. Int. Ed. 2001, 40, 2004–2021; b) V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless,
[5] C. Qin, P. Feng, Y. Ou, T. Shen, T. Wang, C. Qin, N. Jiao, Angew. Chem. 2012, 125, 8089 – 8092; Angew. Chem. Int. Ed. 2013, 52, 6677 – 6680.
[6] C. Qin, P. Feng, Y. Ou, T. Shen, T. Wang, N. Jiao, Angew. Chem. 2013, 125, 8004 – 8008; Angew. Chem. Int. Ed. 2013, 52, 7850 – 7854.

[7] P. A. S. Smith, J. Am. Chem. Soc. 1948, 70, 320 – 323.
[8] a) E. L. Fikes, H. Shechter, J. Org. Chem. 2009, 74, 471 – 474; b) G. L. Milligan, C. J. Mossman, J. Aubé, J. Am. Chem. Soc. 1995, 117, 10449 – 10459; c) O. Gutierrez, J. Aubé, D. J. T allotted, J. Org. Chem. 2012, 77, 640 – 647.

[9] F. Chen, C. Qin, Y. Cui, N. Jiao, Angew. Chem. 2011, 123, 11689 – 11693; Angew. Chem. Int. Ed. 2011, 50, 11487 – 11491.

[10] N. Okamoto, M. Ishikura, R. Yanada, Org. Lett. 2013, 15, 2571 – 2573.
[11] a) C. Nieto-Oberhuber, S. López, A. M. Echavarren, J. Am. Chem. Soc. 2005, 127, 6178 – 6179; b) E. Herrero-Gómez, C. Nieto-Oberhuber, S. López, J. Benet-Buchholz, A. M. Echavarren, Angew. Chem. 2006, 118, 5581 – 5585; Angew. Chem. Int. Ed. 2006, 45, 5455 – 5459; c) P. Pérez-Galán, N. Delpoint, E. Herrero-Gómez, F. Mascaro, A. M. Echavarren, Chem. Eur. J. 2010, 16, 5324 – 5332.

[12] For safety issues on the use of TMSN 3, and generation of hydrazoic acid, see: F. González-Bobes, N. Kopp, L. Li, J. Deerb Berg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm, M. Hrytsak, Org. Process Res. Dev. 2012, 16, 2051 – 2057.

[13] CCDC 960733 (9a), CCDC 960734 (9b), CCDC 960735 (9c) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[14] Only one precedent exists for the structure of the somewhat related neutral complex [(C,F)Au(1-benzyltelluride)], in which the tetrathiozole is also bound through 4N- W. F. Gabrielli, S. D. Nagai, M. Nell, S. Cronje, H. G. Ruubenheimer, Polyhedron 2012, 34, 188 – 197.

[15] a) C. Nieto-Oberhuber, S. López, M. P. Muñoz, D. J. Cárdenas, E. Buhuel, C. Nevado, A. M. Echavarren, Angew. Chem. 2005, 117, 6302 – 6304; Angew. Chem. Int. Ed. 2005, 44, 6146 – 6148; b) C. Obradors, A. M. Echavarren, Chem. Eur. J. 2013, 19, 3547 – 3551; c) A. Homs, C. Obradors, D. Leboeuf, A. M. Echavarren, submitted.

[16] For safety issues on the use of TMSN 3 and generation of hydrazoic acid, see: F. González-Bobes, N. Kopp, L. Li, J. Deerb erg, P. Sharma, S. Leung, M. Davies, J. Bush, J. Hamm, M. Hrytsak, Org. Process Res. Dev. 2012, 16, 2051 – 2057.

[17] CCDC 960733 (9a), CCDC 960734 (9b), CCDC 960735 (9c) contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[18] Only one precedent exists for the structure of the somewhat related neutral complex [(C,F)Au(1-benzyltelluride)], in which the tetrathiozole is also bound through 4N- W. F. Gabrielli, S. D. Nagai, M. Nell, S. Cronje, H. G. Ruubenheimer, Polyhedron 2012, 34, 188 – 197.