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Synthesis of furans and pyrroles via migratory and double migratory cycloisomerization reactions of homopropargylic aldehydes and imines

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Abstract

A novel gold-catalyzed divergent synthesis of furans and pyrroles employing readily available homopropargylic aldehydes and imines have been developed. The regiochemical outcome of this reaction is dependent on the substituent on the terminal alkyne of substrate. Thus, substrates possessing alkyl and aryl substituent at the alkyne moiety produce 2,3,5-substituted furans and pyrroles via a migratory cycloisomerization reaction. Whereas, their silicon analogues are capable to undergo a double migratory process leading to 2,3,4-substituted heterocycles.

Keywords

Cycloisomerization; Heterocycles; Double migration; Silicon migration; Gold catalyst

Furans and pyrroles are highly important motifs exist in a broad range of biologically active natural products¹ and drugs.² They also have broad applications as synthetic intermediates³ and are widely used in material science.⁴ Accordingly, a vast number of efficient methodologies toward these important scaffolds have been developed.^{1a,5} Among these methods, the transition metal-catalyzed migratory cycloisomerization reaction is one of the powerful approaches, which offers mild and selective assembly of furans and pyrroles with a diverse substitution pattern.⁶ Readily available homopropargylic ketones and imines have been employed in migratory cascade reactions^{5a,6a} giving access to a variety of heterocycles (Scheme 1). For instance, Kirsch reported⁷ a platinum-catalyzed cascade reaction of **1** toward 3(2H)-furanones and 3-pyrrolones **2** proceeding via a pinacol-type 1,2-alkyl migration⁸ (eq. 1). Moreover, Tang and Shi reported synthesis of densely-substituted pyrroles **4** from the rhodium-catalyzed reaction of propargylic imines **3**, where one of the substituents of the heterocyclic core is formed via a 1,2-alkyl migration from the adjacent carbon (eq. 2).⁹ Recently, Zhang disclosed a divergent reactivity of ketones **5** in the presence

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of gold catalysts, where a selective 1,2-alkyl migration to the neighboring carbon affords dihydrofurans **6** or furans **7** (eq. 3).¹⁰ Herein, we report a mild and regiodivergent reaction of homopropargylic aldehydes and imines **8** in the presence of gold catalysts towards heterocycles **9** and **10**. Thus, a gold-catalyzed *migratory cycloisomerization* of **8** ($R^1 = \text{Alk/Ar}$) produces 2,3,5-substituted heterocycles **9**. Whereas, employment of silylated **8** ($R^1 = \text{SiR}_3$) affords 2,3,4-substituted furans and pyrroles **10** proceeding via a *double migratory cycloisomerization* reaction (eq. 4).

In continuation of our interest in development of cycloisomerization reactions toward synthesis of densely substituted heterocycles,¹¹ we aimed at employing aldehyde **8** possessing a cyclopentyl group (Scheme 1, $X = \text{O}$, $R^1 = \text{Ph}$, $R^2 = R^3 = (\text{CH}_2)_4$) in the transition metal-catalyzed migratory cascade reaction. It was hypothesized that cyclization of the latter in the presence of a metal catalyst would be accompanied with a five-to-six-membered ring expansion¹² and therefore producing the bicyclic fused furan **9** (Scheme 1, $X = \text{O}$, $R^1 = \text{Ph}$, $R^2 = R^3 = (\text{CH}_2)_4$). Our optimization study indicated that the use of the cationic gold catalyst,¹³ such as triphenylphosphine gold with hexafluoroantimonate counter ion, was the best choice. Thus, we explored the scope of this migratory cycloisomerization. Hence, aldehydes **8a-c** possessing phenyl, electron poor aryl, as well as alkyl substituents at the terminal alkyne position underwent a five-to-six-membered ring expansion during the cycloisomerization process to afford furans **9a-c** in good to excellent yields (entry 1-3). Importantly, this reaction is not limited to cyclic substrates only. Thus, by employing 2,2-diphenyl homopropargyl aldehyde **8d**, a phenyl group migration occurs smoothly to afford the triarylated furan **9d** in an excellent yield (entry 4). Expectedly,¹² a phenyl migration took place over the methyl- and benzyl group migration in cycloisomerization of **8e** and **8f** to furnish **9e** and **9f** in moderate yields (entries 5 and 6). Moreover, tetrasubstituted pyrroles can also be synthesized using 2,2-substituted homopropargylic imines under these reaction conditions. Therefore, the five-to-six-membered ring expansion of imines **8g** and **8h** proceeded smoothly during cyclization to provide pyrroles **9g** and **9h** in good yields (entry 7 and 8). Expectedly, a phenyl group migration occurred preferably over the methyl- and benzyl group migrations to produce pyrroles **9i** and **9j** selectively in good yields (entry 9 and 10).

Next, we hypothesized that employing homopropargylic aldehyde **8** possessing a silicon terminus (Scheme 1, $X = \text{O}$, $R^1 = \text{SiMe}_3$, $R^2 = R^3 = (\text{CH}_2)_4$) would enable a 1,2-migration of silicon group during the cyclization process.¹⁴ This 1,2-alkyl-/Si-double migratory cascade¹⁵ would allow synthesis of 2,3,4-trisubstituted fused furan **10**. Indeed, it was found that cationic $(\text{C}_6\text{F}_5)_3\text{PAuSbF}_6$ catalyst¹⁶ efficiently catalyzes this reaction (Table 2).¹⁷ Thus, homopropargylic aldehyde **8k-m** underwent a facile ring expansion/trimethyl-, triethyl-, and *t*-butyldimethylsilyl migration-cycloisomerization cascade to efficiently produce furans **10k-m**, respectively. Aldehyde **8n** possessing a strained four-membered ring produced bicyclic furan **10n** in a reasonable yield (entry 4). Notably, employment of *t*-Bu- and Ph-protected imines **8o** and **8p** in this double migratory process afforded silylated fused pyrroles **10o** and **10p**.

We propose the following plausible mechanism for these cascade reactions (Scheme 2). First, the π -philic gold catalyst activates substrate **8**, which upon the following nucleophilic attack of carbonyl at the activated alkyne moiety of **A** in a *5-endo-dig* fashion produces cyclic oxonium intermediate **B**. A 1,2- R^2 migration in the latter takes place to generate an allylic cation **C**, which upon proton loss furnishes the key furyl gold intermediate **D**. In the case of $G=Alk$ or Ar , a protodemetalation (α -protonation) of **D** takes place to produce 2,3,5-trisubstituted furan **9**. Whereas, the β -protonation of the furyl gold species **D** occurs¹⁴ when $G=SiR_3$ to furnish **E**, in which the positive charge at the carbene carbon is stabilized by the silicon atom.¹⁸ A 1,2-silicon- over hydrogen 1,2-migration in the latter takes place¹⁴ to form **F**, which upon aromatization affords 2,3,4-trisubstituted furan **10**.

In summary, two complementary gold-catalyzed cycloisomerization reaction protocols of homopropargylic aldehydes and imines toward differently substituted furans and pyrroles have been developed. The regiochemical outcome depends on the substituent at the terminal alkyne moiety of the substrates. Thus, employment of homopropargylic aldehydes and imines possessing alkyl and aryl substituent at the alkyne moiety produces 2,3,5-substituted heterocycles via a migratory cycloisomerization reaction. Whereas, substrates possessing a silicon atom at the terminal position of alkyne undergo a double migratory cascade to afford 2,3,4-substituted furans and pyrroles.¹⁹

Acknowledgments

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References and notes

1. a Katritzky, AR.; Ramsden, CA.; Scriven, EFV.; Taylor, RJK., editors. Comprehensive Heterocyclic Chemistry III. Vol. 3 and 11. Elsevier; Oxford, U.K.: 2008. b Dean, FM. Naturally Occurring Oxygen Ring Compounds. Butterworths; London: 1963. p. 1Chapter 1
2. a Estevez V, Villacampa M, Menendez JC. Chem. Soc. Rev. 2010; 39:4402. [PubMed: 20601998] b hu LL, Luo JS, Hong R. Org. Lett. 2014; 16:2162. [PubMed: 24684554]
3. a Gribble GW, Saulnier MG, Pelkey ET, Kishbaugh TLS, Yanbing L, Jiang J, Trujillo HA, Keavy DJ, Davis DA, Conway SC, Switzer FL, Roy S, Silva RA, Obaza-Nutaitis JA, Sibi MP, Moskalev NV, Barden TC, Chang L, Habeski WM, Peleman B, Sponholtz WR,III, Chau RW, Allison BD, Garaas SD, Sinha MS, McGowan MA, Reese MR, Harpp KS. Curr. Org. Chem. 2005; 9:1493.b Evano G, Blanchard N, Toumi M. Chem. Rev. 2008; 108:3054. [PubMed: 18698737] c Isambert N, Lavilla R. Chem.—Eur. J. 2008; 14:8444. [PubMed: 18576454] d Chinchilla R, Nájera C, Yus M. Chem. Rev. 2004; 104:2667. [PubMed: 15137804]
4. a Novak P, Muller K, Santhanum KSV, Haas O. Chem. Rev. 1997; 97:207. [PubMed: 11848869] b Descalzo AB, Xu HJ, Xue ZL, Hoffmann K, Shen Z, Weller MG, You XZ, Rurack K. Org. Lett. 2008; 10:1581. [PubMed: 18355071] c Lin JT, Chen PC, Yen YS, Hsu YC, Chou HH, Yeh MCP. Org. Lett. 2009; 11:97. [PubMed: 19067570]
5. a Gulevich AV, Dudnik AS, Chernyak N, Gevorgyan V. Chem. Rev. 2013; 113:3084. [PubMed: 23305185] b Estevez V, Villacampa M, Menendez JC. Chem. Soc. Rev. 2014; 43:4633. [PubMed: 24676061]
6. a Dudnik AS, Chernyak N, Gevorgyan V. Aldrichim. Acta. 2010; 43:37.b Obradors C, Echavarren AM. Acc. Chem. Res. 2014; 47:902. [PubMed: 24175907] c Fensterbank L, Malacria M. Acc. Chem. Res. 2014; 47:953. [PubMed: 24564512]
7. a Kirsch SF, Binder JT, Liebert C, Menz H. Angew. Chem., Int. Ed. 2006; 45:5878.b Binder JT, Crone B, Kirsch SF, Liebert C, Menz H. Eur. J. Org. Chem. 2007;1636.c Umland KD, Palisse A,

- Haug TT, Kirsch SF. *Angew. Chem., Int. Ed.* 2011; 50:9965. d Zhang ZJ, Ren ZH, Wang YY, Guan ZH. *Org. Lett.* 2013; 15:4822. [PubMed: 23988157]
8. Umland KD, Kirsch SF. *Synlett.* 2013; 24:1471. For a review, see:
9. Chen GQ, Zhang XN, Wei Y, Tang XY, Shi M. *Angew. Chem., Int. Ed.* 2014; 53:8492.
10. a Li WB, Li YY, Zhou GH, Wu XS, Zhang JL. *Chem-Eur J.* 2012; 18:15113. [PubMed: 23042122] b Li WB, Li YY, Zhang JL. *Chem.-Eur. J.* 2010; 16:6447. [PubMed: 20437431]
11. a Kel'in AV, Sromek AW, Gevorgyan V. *J. Am. Chem. Soc.* 2001; 123:2074. [PubMed: 11456838] b Kel'in AV, Gevorgyan V. *J. Org. Chem.* 2002; 67:95. [PubMed: 11777444] c Kim JT, Kel'in AV, Gevorgyan V. *Angew. Chem., Int. Ed.* 2003; 42:98. d Sromek AW, Kel'in AV, Gevorgyan V. *Angew. Chem., Int. Ed.* 2004; 43:2280. e Schwier T, Sromek AW, Yap DML, Chernyak D, Gevorgyan V. *J. Am. Chem. Soc.* 2007; 129:9868. [PubMed: 17658805] f Dudnik AS, Sromek AW, Rubina M, Kim JT, Kel'in AV, Gevorgyan V. *J. Am. Chem. Soc.* 2008; 130:1440. [PubMed: 18173272]
12. a Crone B, Kirsch SF. *Chem. –Eur. J.* 2008; 14:3514. [PubMed: 18318026] b Dudnik AS, Gevorgyan V. *Angew. Chem., Int. Ed.* 2007; 46:5195. c Garayalde D, Nevado C, Beilstein J. *Org. Chem.* 2011; 7:767. [PubMed: 21772928]
13. a Hashmi AS. K. *Acc. Chem. Res.* 2014; 47:864. For recent reviews of homogeneous gold-catalyzed reactions, see: b Zhang L. *Acc. Chem. Res.* 2014; 47:877. [PubMed: 24428596] c Wang YM, Lackner AD, Toste FD. *Acc. Chem. Res.* 2014; 47:889. [PubMed: 24228794] d Zhang DH, Tang XY, Shi M. *Acc. Chem. Res.* 2014; 47:913. [PubMed: 24168021] e Furstner A. *Acc. Chem. Res.* 2014; 47:925. [PubMed: 24279341] f Liu LP, Hammond GB. *Chem. Soc. Rev.* 2012; 41:3129. [PubMed: 22262401] g Marco-Contelles J, Soriano E. *Chem.-Eur. J.* 2007; 13:1350. [PubMed: 17200921] h Rao W, Koh MJ, Li D, Hirao H, Chan PWH. *J. Am. Chem. Soc.* 2013; 135:7926. [PubMed: 23627597] i Cao ZP, Gagosz F. *Angew. Chem., Int. Ed.* 2013; 52:9014. j Hofer M, Gomez-Bengoa E, Nevado C. *Organometallics.* 2014; 33:1328. l Pagar VV, Jadhav AM, Liu RS. *J. Am. Chem. Soc.* 2011; 133:20728. [PubMed: 22128862]
14. Dudnik AS, Xia YZ, Li YH, Gevorgyan V. *J. Am. Chem. Soc.* 2010; 132:7645. [PubMed: 20476771]
15. a Kazem Shiroodi R, Gevorgyan V. *Chem. Soc. Rev.* 2013; 42:4991. [PubMed: 23443274] b Kazem Shiroodi R, Dudnik AS, Gevorgyan V. *J. Am. Chem. Soc.* 2012; 134:6928. [PubMed: 22489740] c Gronnier C, Boissonnat G, Gagosz F. *Org. Lett.* 2013; 15:4234. [PubMed: 23909764]
16. Istrate FM, Gagosz F. *Org. Lett.* 2007; 9:3181. [PubMed: 17608434]
17. The optimized reaction conditions for migratory cascade reaction (Table 1) did not work for the double migratory process (Table 2). Thus, it was found that the highly electrophilic (C₆F₅)₃PAuSbF₅ catalyst under more diluted reaction conditions was the best
18. a Danheiser RL, Carini DJ, Basak A. *J. Am. Chem. Soc.* 1981; 103:1604. For leading examples about β -silicon effect, see: b Wierschke SG, Chandrasekhar J, Jorgensen WL. *J. Am. Chem. Soc.* 1985; 107:1496.
19. a General Procedure for the migratory cycloisomerization reaction of 8 to furans and pyrroles 9: An oven dried 1 mL V-shape vial equipped with magnetic stir bar was loaded with commercially available chloro(triphenylphosphine) gold (5 mol%, 12.5 mg) and silver hexafluoroantimonate (5 mol%, 8.5 mg) in the glove box. 1,2-dichloroethane (500 μ L) was then added and reaction mixture was stirred for 5 min at room temperature. Homopropargylic aldehydes or imines 8 (1.0 equiv, 0.5 mmol) as a solution in 1,2-dichloroethane (500 μ L) was added through cannula and the reaction mixture stirred at room temperature until judged completed by GC/MS. The reaction mixture was then passed through Celite[®], solvents were removed under reduced pressure, and the residue was purified by flash chromatography using silica gel (Hex/EtOAc= 40/1) to give furans or pyrroles 9. Representative example: 9e: ¹H NMR (500 MHz, CDCl₃) δ ppm 7.75 (d, J = 7.4 Hz, 4 H), 7.47 (t, J = 7.8 Hz, 2 H), 7.42 (t, J = 7.8 Hz, 2 H), 7.35-7.24 (m, 2H), 6.64 (s, 1 H), 2.36 (s, 3 H). ¹³C NMR (126 MHz, CDCl₃) δ ppm 151.7, 148.2, 131.8, 130.8, 128.7, 128.6, 127.2, 126.7, 125.3, 123.7, 118.7, 110.8, 12.2. b General Procedure for the double migratory cycloisomerization reaction of 8 to furans and pyrroles 10: An oven dried 20 mL round bottom flask equipped with magnetic stir bar was loaded with commercially available chloro[tris(2,3,4,5,6-pentafluorophenyl)-phosphine] gold (5 mol%, , 19.1 mg) and silver hexafluoroantimonate (5 mol%, 8.5 mg) in the glove box. 1,2-dichloroethane (11 mL) was then added and reaction mixture was stirred for 5 min

at room temperature. Homopropargylic aldehyde or imine 8 (1.0 equiv, 0.5 mmol) as a solution in 1,2-dichloroethane (1.5 mL) was added through cannula and the reaction mixture stirred at room temperature until judged completed by GC/MS. The reaction mixture was then passed through Celite[®], solvents were removed under reduced pressure, and the residue was purified by flash chromatography using silica gel (pure hexanes) to give furans or pyrroles 10. Representative example: 10k: ¹H NMR (500 MHz, CDCl₃) δ ppm 7.15 (s, 1 H), 2.64 - 2.55 (m, 2 H), 2.48 (tt, J = 1.8, 6.1 Hz, 2 H), 1.88 - 1.80 (m, 2 H), 1.79 - 1.72 (m, 2 H), 0.23 (s, 9 H). ¹³C NMR (126 MHz, CDCl₃) δ ppm 151.2, 145.1, 120.3, 118.7, 23.3, 23.1, 23.0, 22.9, - 0.7

Scheme 1.

Cycloisomerization of homopropargylic systems involving a 1,2-migration

Scheme 2.

Proposed Mechanism for the migratory and double migratory cascade reactions

Table 1

Scope of the migratory cycloisomerization reaction

Entry	Substrate		Product		Yield % ^{a,b}
1		8a		9a	90
2		8b		9b	80
3		8c		9c	71
4		8d		9d	90
5		8e		9e	56
6		8f		9f	58
7		8g		9g	74
8		8h		9h	72
9		8i		9i	70
10		8j		9j	71

^a Isolated Yield.
^b Reactions were performed in 0.5 mmol scale