

Aliphatic Acetylenic Homocoupling Catalyzed by a Novel Combination of AgOTs–CuCl₂–TMEDA and Its Application for the Solid-Phase Synthesis of Bis-benzo[*b*]furan-Linked 1,3-Diynes

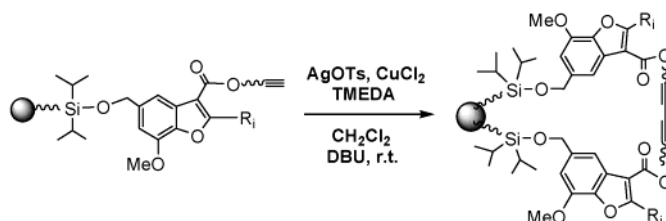
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Received January 17, 2003

ABSTRACT



A novel catalytic system of AgOTs–CuCl₂–TMEDA is described for the homocoupling of aliphatic acetylenes on solid support. It is the first observation that Ag^I's activating triple bond could facilitate Cu^{II}-mediated oxidative acetylenic homocoupling. This study provides an efficient way to synthesize a diversified symmetrical bis-benzo[*b*]furan-linked 1,3-diyne library on solid support.

As a powerful tool in molecular construction, acetylenic homocoupling has been extensively studied^{1a} since Glaser's pioneering work^{1b,c} in 1869. The Glaser–Hay coupling^{1d} and the Eglinton–Galbraith method^{1e–g} remain the most successful techniques in addition to the recently improved palladium-catalyzed homocoupling.^{1h,i}

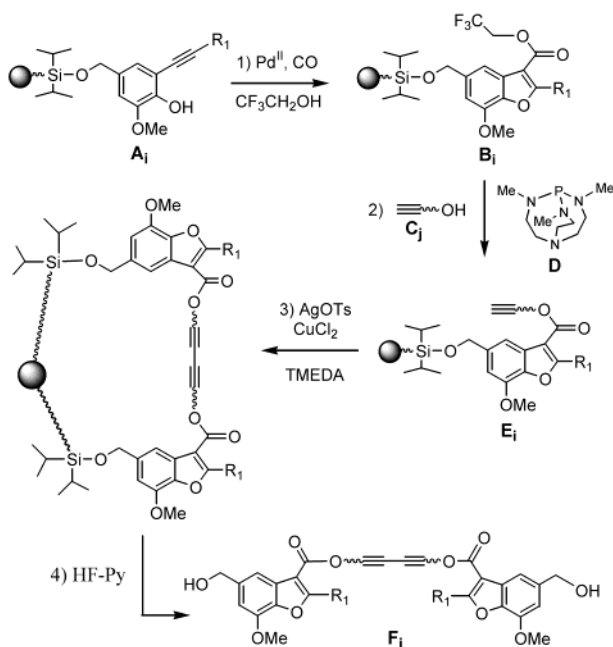
However, no study on polymer-supported aliphatic acetylenic homocoupling has hitherto been reported. During the course of our systematic studies^{2a,b} focusing on Pd- and Cu-mediated couplings and domino reactions on macrobeads,^{2c} we primarily observed that the on-bead aromatic terminal acetylenes easily undergo homocoupling under the Sonogashira conditions.^{2a} This evidence confirmed our assumption that polymer-supported acetylenic homocoupling could be an important viable path to construct a symmetrical dimeric scaffold,^{3a} which is of significant interest due to its unique

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(1) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, 39, 2634–2657 and references therein. (b) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, 2, 422–424. (c) Glaser, C. *Ann. Chem. Pharm.* **1870**, 154, 137–171. (d) Hay, A. S. *J. Org. Chem.* **1962**, 27, 3320–3321. (e) Eglinton, G.; Galbraith, A. R. *Chem. Ind. (London)* **1956**, 737–738. (f) de Meijere, A.; Kozhushkov, S. I. *Top. Curr. Chem.* **1999**, 201, 1–42. (g) Haley, M. M.; Pak, J. J.; Brand, S. C. *Top. Curr. Chem.* **1999**, 201, 81–130. (h) Liu, Q.; Burton, D. J. *Tetrahedron Lett.* **1997**, 38, 4371–4374. (i) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, 67, 1969–1971.

(2) (a) Liao, Y.; Fathi, R.; Reitman, M.; Zhang, Y.; Yang, Z. *Tetrahedron Lett.* **2001**, 42, 1815–1818. (b) Liao, Y.; Reitman, M.; Zhang, Y.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, 4, 2607–2609. (c) Tallarico, J. A.; Depew, K. M.; Pelish, H. E.; Westwood, N. J.; Lindsley, C. W.; Shair, M. D.; Schreiber, S. L.; Foley, M. A. *J. Comb. Chem.* **2001**, 3, 312–318.

Scheme 1^a

^a Conditions: (1) CO balloon, CF₃CH₂OH, Pd(PPh₃)₂Cl₂-dppp (1.2 equiv), CsOAc, DMF, 45 °C, 24 h; (2) Superbase **D**, alkynol **C_j**, THF, rt, 48 h; (3) CuCl₂ (1.1 equiv), AgOTs (1.1 equiv), TMEDA (*N,N,N',N'*-tetramethylethylenediamine), DBU, CH₂Cl₂, rt, 17 h; (4) HF/Py 5% in THF, rt, 1 h; TMSOMe, 0.5 h.

function as a modulator of cellular processes^{3b} and its potential contribution to protein interaction by providing an extra binding domain.^{3c} Unfortunately, none of the known methods¹ being tested are applicable for the on-bead aliphatic acetylenic homocoupling. This challenge had not been realized until we developed a unique AgOTs–CuCl₂–TMEDA combination that proved to be a superior system in both solution and solid phase, thereby providing the possibility for the acetylenic homocoupling on solid support.

Considering the frequent occurrence of di- and oligoacetylene moieties,^{4a,b} as well as benzofuran skeleton^{4c,d} in natural products which possess intriguing biological activities,^{4c,d} we became increasingly interested in constructing a dimeric benzofuran scaffold by exploring the acetylenic homocoupling on solid support for future combinatorial library construction.

As illustrated in Scheme 1, the key intermediates **E_i** were generated via a Pd^{II}-mediated cascade carbonylative annulation^{2b} of **A_i** to give activated esters **B_i**, followed by a Verkade superbase **D**⁵ catalyzed transesterification with various alkynols **C_j**.

The subsequent on-bead acetylenic homocoupling (**E_i** to **F_i**) encountered unexpected difficulties. During the model study (**C_j** = 4-pentyn-1-ol, **R_i** = tolyl, *i* = 2, Scheme 1),

(3) (a) Clemons, P. A. *Curr. Opin. Chem. Biol.* **1999**, *3*, 112–115. (b) Diver, S. T.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 5106–5109 and references therein. (c) Nicolaou, K. C.; Hughes, R.; Cho, S.-Y.; Winssinger, N.; Smethurst, C.; Labischinski, H.; Endermann, R. *Angew. Chem., Int. Ed.* **2000**, *39*, 3823–3828 and references therein.

Table 1. Relative Efficiency of Various Methods for the On-Bead Aliphatic Homocoupling of **E₂** to **F₂**

entry	acetylenic homocoupling conditions	E₂/F₂ (conv, %)
1	Pd ^{II} /Pd ⁰ , CuI, oxidants, bases, solvents, rt	>60:40 (<10)
2	Cu(OAc) ₂ , pyridine (DBU), rt to 80 °C	>50:50 (<25)
3	CuCl or CuI, O ₂ , TMEDA or dipyriddy	>70:30 (<20)
4	CuCl ₂ , CuI, TMEDA, DBU, CH ₂ Cl ₂ , rt	50:50 (<20)
5	CuCl ₂ , CuI, AgOAc , TMEDA, DBU CH ₂ Cl ₂ , rt	50:50 (45)
6	CuCl ₂ , CuI, AgOTf , TMEDA, DBU CH ₂ Cl ₂ , rt	40:60 (55)
7	CuCl ₂ , CuI, AgOTs , TMEDA, DBU CH ₂ Cl ₂ , rt	5:85 (85)
8	CuCl₂, AgOTs, TMEDA, DBU, CH₂Cl₂, rt	5:85 (85)
9	Cu(OTf) ₂ , TMEDA, DBU, CH ₂ Cl ₂ , rt	100:0 (0)
10	Cu(OTs) ₂ , TMEDA, DBU, CH ₂ Cl ₂ , rt	100:0 (0)
11	Cu(OTs) ₂ , AgOTs, TMEDA, DBU CH ₂ Cl ₂ , rt	100:0 (0)
12	AgOTs, TMEDA, DBU, CH ₂ Cl ₂ , rt	100:0 (0)

neither the Pd-catalyzed methods^{1h,i,2a} (entry 1 in Table 1) nor the Eglinton–Galbraith method^{1e–g} and Glaser–Hay coupling^{1d} as well as their many variants (entries 2–4 in Table 1) could provide any results with acceptable purities/yields. Prolonging the reaction time only resulted in even poorer purities and yields. This drawback of the on-bead aliphatic acetylenic homocoupling in comparison with its aromatic counterpart^{2a} may derive from the aliphatic terminal alkyne's lower acidity, but higher instability of its diyne product toward transition metals.⁶ Furthermore, the inefficiency was “amplified” by the on-bead reaction which usually is more sluggish and much slower than the solution-phase reaction.⁷

Ag^I could activate the terminal carbon–hydrogen bond by forming a π -complex with the triple bond.^{8a} However, there is no report regarding the role of Ag^I in facilitating acetylene homocoupling. We screened three Ag^I salts and observed a clear activation tendency in the following order: AgOAc < AgOTf < AgOTs (entries 5–7 in Table 1). In the case of AgOTs, the on-bead homocoupling preceded smoothly in a high conversion (85% based on ¹H NMR analysis, entry 7 in Table 1). The prominent activation effect of the AgOTs may come from the much weaker coordinating nature of OTs[–] than that of AcO[–] and TfO[–], which makes the cationic Ag^I more “naked”^{8b} and facilitates its association

(4) (a) Hansen, L.; Boll, P. M. *Phytochemistry* **1986**, *25*, 285–293. (b) Lu, W.; Haji, G. Z.; Aisa, A.; Cai, J. *Tetrahedron Lett.* **1998**, *39*, 9521–9522. (c) Engler, T. A.; LaTessa, K. O.; Lyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755–1769. (d) Pieters, L.; Van Dyck, S.; Gao, M.; Bai, R.; Hamel, E.; Vlietinck, A.; Lemiére, G. *J. Med. Chem.* **1999**, *42*, 5473–5481. (e) Donnelly, D. M. X.; Meegan, M. J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Pergamon Press: New York, 1984; Vol. 4. (f) Erber, S.; Ringshandl, R.; von Angerer, E. *Anti-Cancer Drug Des.* **1991**, *6*, 417. (g) Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W. X.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293. (h) Watanabe, Y.; Yoshiwara, H.; Kanao, M. *J. Heterocycl. Chem.* **1993**, *30*, 445. (i) McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67. (j) Yang, Z.; Liu, H.-B.; Lee, C.-M.; Chang, H.-M.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248.

(5) Ilankumaran, P.; Verkade, J. G. *J. Org. Chem.* **1999**, *64*, 3086–3089. (6) Rossi, R.; Carpita, A.; Bigelli, C. *Tetrahedron Lett.* **1985**, *26*, 523–526.

(7) (a) Hudson, D. J. *Comb. Chem.* **1999**, *1*, 333–360; 403–456. (b) Vaino, A. R.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 579–596.

(8) (a) Ginnebaugh, J. P.; Maki, J. W.; Lewandos, G. S. *J. Organomet. Chem.* **1980**, *190*, 403–416. (b) Tsuji, J. *Acc. Chem. Res.* **1973**, *6*, 8–15. (c) Jacobs, L. A.; Van Vuuren, C. P. *J. Thermochim. Acta* **1988**, *127*, 399–402.

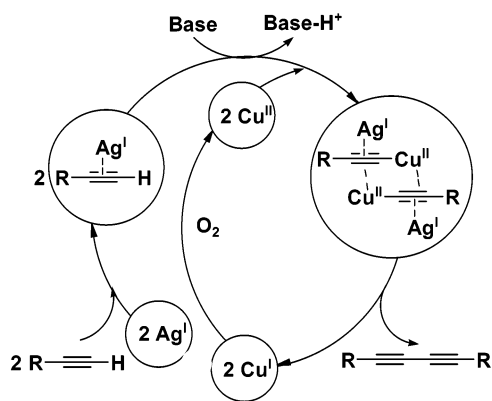


Figure 1. Proposed mechanism of the acetylenic homocoupling.

with the acetylene, and as a consequence activates the triple bond more efficiently.

To confirm the true active species, $\text{Cu}(\text{OTf})_2$ (entry 9), $\text{Cu}(\text{OTs})_2$ (entry 10), and $\text{Cu}(\text{OTs})_2/\text{AgOTs}$ (entries 11 and 12) were also tested. As a result, only the starting substrate **E**₂ was recovered in each case. This demonstrates that CuCl_2 is required and its Cl^- exchange with OTs^- from AgOTs may not occur since a soluble enthalpy-driven Ag^{I} –TMEDA complex may be formed in CH_2Cl_2 ,^{8c} which prevents AgCl precipitation.

A plausible mechanism (Figure 1) of Ag^{I} -activated Cu^{II} -catalyzed oxidative acetylenic homocoupling may start from the π -complexing of Ag^{I} with the triple bond, activating the terminal acetylene so as to accelerate the deprotonation by the base, facilitating the further formation of a possible dinuclear Cu^{II} acetylide complex,^{1a} which collapses directly to the homocoupling product and Cu^{I} . According to the mechanism, Cu^{I} is not necessary as anticipated (entry 8).

To assess the general applicability of the combined catalytic system AgOTs – CuCl_2 –TMEDA, eight on-bead terminal alkynes **E**_i (Scheme 1) underwent smooth homocoupling to generate the corresponding **F**_i, and the results are shown in Table 2.¹⁰ For the six products with a bridge of 10 carbons in the center (**F**₁–**F**₆), the conversion/purity is around 85% to 90%. For the product with a bridge of eight carbons in the center (**F**₇), the conversion/purity is a little lower, around 70%. For the product with a bridge of eight carbons in the center but containing branch substitution (**F**₈), the conversion remains 80%.

All the results were confirmed by both LC–MS and ^1H NMR analyses. To accelerate the homocoupling on the

Table 2. Results of the $\text{AgOTs}/\text{CuCl}_2/\text{TMEDA}$ -Promoted On-Bead Aliphatic Acetylenic Homocoupling

entry	homocoupling products	purity % ^[a]
F ₁		90%
F ₂		85%
F ₃		90%
F ₄		90%
F ₅		90%
F ₆		85%
F ₇		70%
F ₈		80% or 70% ^[b]

^a Purity was estimated by ^1H NMR analysis. ^b The same unreactive impurity (10%) exists in both **E**₈ and **F**₈, which does not affect the conversion (80%) but does decrease the purity (70%).

macrobeads and to avoid side reactions, a stoichiometric amount of AgOTs – CuCl_2 was utilized. Prolonging the reaction time over 20 h in order to drive the homocoupling to completion only resulted in lower conversion/yield partly due to the instability of the aliphatic diyne. In homogeneous solution-phase synthesis the homocoupling of 4-pentyn-1-ol could be accomplished in almost quantitative yield in 1 h at 20 °C by using 0.1 equiv of the AgOTs – CuCl_2 –TMEDA under a balloon pressure of pure oxygen. In comparison, the Pd-catalyzed method¹ⁱ and the Hay coupling^{1d} only led to 5% and 22% conversions, respectively, employing the similar loading of catalysts in 1 h at 20 °C. The Eglinton–Galbraith method^{1e–g} gave a 90% yield in 1 h; however, excess $\text{Cu}(\text{OAc})_2$ had to be employed at 50 °C. Clearly, in comparison with the old methods in both solid and solution phase, the new system exhibited its superiority, which turned out to be a determining factor in the case of the on-bead aliphatic acetylenic homocoupling in which the reaction rate is extremely critical to influence the final purity and yield.

In summary, this paper describes a novel solid-supported aliphatic acetylenic homocoupling by developing a novel superior AgOTs – CuCl_2 –TMEDA system. Also, it is the first observation that an Ag^{I} -activating triple bond could facilitate

(9) Blackwell, H. E.; Clemons, P. A.; Schreiber, S. L. *Org. Lett.* **2001**, 3, 1185–1188.

(10) The procedure for solid-phase synthesis is provided in the Supporting Information, and a typical procedure for the solution-phase synthesis is described below. The CuCl_2 (13.4 mg, 0.1 equiv), AgOTs (27.9 mg, 0.1 equiv), TMEDA (0.1 mL), DBU (0.5 mL), and CH_2Cl_2 (2 mL) were mixed under the balloon pressure of O_2 and stirred for 0.5 h before the 4-pentyn-1-ol (84 mg, 1.0 equiv) was added. The clear deep green solution was stirred for another 1 h and filtered through a short plug of silica gel with ethyl acetate. The filtrate was washed with a saturated NH_4Cl solution. Removing the ethyl acetate resulted in deca-4,6-diyne-1,10-diol as a colorless semisolid (78 mg, 94% yield).

Cu^{II}-mediated oxidative acetylenic homocoupling. We thereby solved an obstacle in translating this classical reaction onto the solid phase. Thus, we have developed a valuable approach to potentially make diversified symmetrical molecules efficiently by means of the site–site interaction⁹ within the polymer. Indeed, the new system developed herein allows diverse substitutions, as well as 1,3-diyne bridges with different lengths and branches to be integrated into the final

scaffold, and as a result is capable of leading to generation of a novel biologically interesting symmetrical bis-benzo-[*b*]furan-linked 1,3-diyne molecules.

Supporting Information Available: Experimental procedures and NMR and LC–MS spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL030009G