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Aliphatic Acetylenic Homocoupling Catalyzed by a Novel Combination of AgOTs–$CuCl_2$–TMEDA and Its Application for the Solid-Phase Synthesis of Bis-benzo[*b*]furan-Linked 1,3-Diynes

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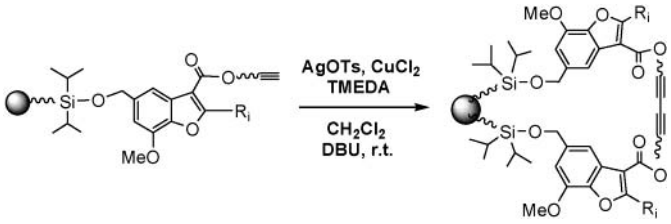
ABSTRACT



A novel catalytic system of AgOTs–$CuCl_2$–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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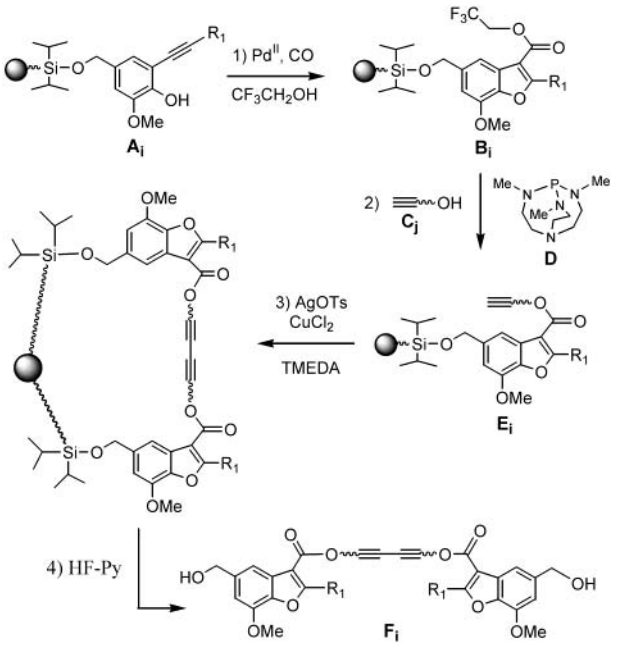
Scheme 1[a]



[a] Conditions: (1) CO balloon, CF_3CH_2OH, $Pd(PPh_3)_2Cl_2$−dppp (1.2 equiv), CsOAc, DMF, 45 °C, 24 h; (2) Superbase **D**, alkynol $\mathbf{C_j}$, THF, rt, 48 h; (3) $CuCl_2$ (1.1 equiv), AgOTs (1.1 equiv), TMEDA (*N*,*N*,*N*,*N*-tetramethylethylenediamine), DBU, CH_2Cl_2, 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 methods[1] being tested are applicable for the on-bead aliphatic acetylenic homocoupling. This challenge had not been realized until we developed a unique AgOTs−$CuCl_2$−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 $\mathbf{E_i}$ were generated via a Pd^{II}-mediated cascade carbonylative annulation[2b] of $\mathbf{A_i}$ to give activated esters $\mathbf{B_i}$, followed by a Verkade superbase **D**[5] catalyzed transesterification with various alkynols $\mathbf{C_j}$.

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

Table 1. Relative Efficiency of Various Methods for the On-Bead Aliphatic Homocoupling of $\mathbf{E_2}$ to $\mathbf{F_2}$

entry	acetylenic homocoupling conditions	$\mathbf{E_2}/\mathbf{F_2}$ (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 dipyridyl	>70:30 (<20)
4	$CuCl_2$, CuI, TMEDA, DBU, CH_2Cl_2, rt	50:50 (<20)
5	$CuCl_2$, CuI, **AgOAc**, TMEDA, DBU CH_2Cl_2, rt	50:50 (45)
6	$CuCl_2$, CuI, **AgOTf**, TMEDA, DBU CH_2Cl_2, rt	40:60 (55)
7	$CuCl_2$, CuI, **AgOTs**, TMEDA, DBu CH_2Cl_2, rt	5:85 (85)
8	**$CuCl_2$, AgOTs, TMEDA, DBU, CH_2Cl_2, rt**	**5:85 (85)**
9	$Cu(OTf)_2$, TMEDA, DBU, CH_2Cl_2, rt	100:0 (0)
10	$Cu(OTs)_2$, TMEDA, DBU, CH_2Cl_2, rt	100:0 (0)
11	$Cu(OTs)_2$, AgOTs, TMEDA, DBU CH_2Cl_2, rt	100:0 (0)
12	AgOTs, TMEDA, DBU, CH_2Cl_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

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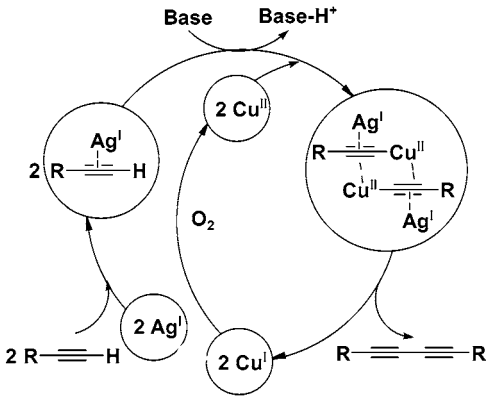


Figure 1. Proposed mechanism of the acetylenic homocoupling.

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

To confirm the true active species, $Cu(OTf)_2$ (entry 9), $Cu(OTs)_2$ (entry 10), and $Cu(OTs)_2$/AgOTs (entries 11 and 12) were also tested. As a result, only the starting substrate **E₂** 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.

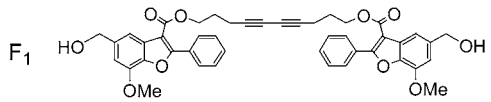
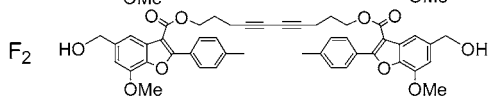
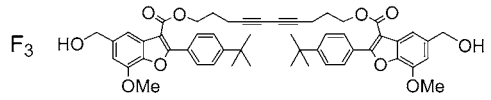
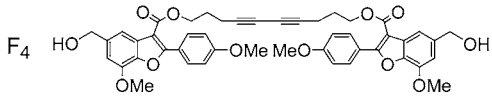
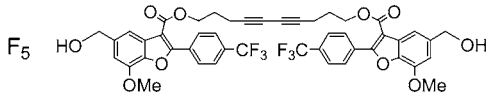
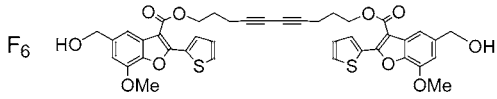
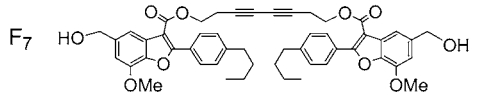
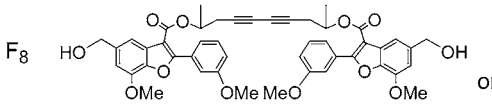
A plausible mechanism (Figure 1) of Ag^I-activated Cu^{II}-catalyzed oxidative acetylenic homocoupling may start from the π-complexing of Ag^I with the triple bond, activating the terminal acetylene so as to accelerate the deprotonation by the base, facilitating the further formation of a possible dinuclear Cu^{II} acetylide complex,[1a] which collapses directly to the homocoupling product and Cu^I. According to the mechanism, CuI 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 ^{1}H NMR analyses. To accelerate the homocoupling on the 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 method[1i] 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 $Cu(OAc)_2$ 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 aecetylenic 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

Table 2. Results of the AgOTs/$CuCl_2$/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 ^{1}H 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%).

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(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 interaction[9] 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.

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