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The Unprecedented Cobalt-Catalysed Oxidative Glaser Coupling under Reductive Conditions

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Abstract: The cobalt-catalysed Glaser-type coupling of terminal alkynes was achieved utilising nitrobenzene as a stoichiometric oxidising agent under reductive conditions. The proposed electron transfer from zinc powder to a nitrobenzene coordinated to the cobalt centre initiates the coupling of the coordinated alkynes. Other aryl-, alkenyl-, alkyl-, and silylacetylenes besides phenylacetylene could also be coupled to generate the 1,3-diynes in moderate to very good yields.

Key words: alkyne, cobalt, Glaser coupling, oxidation, diynes

The synthesis of symmetrical diynes by oxidative coupling of terminal alkynes has a long tradition in organic synthesis starting with the first observation of a copperinitiated process by Glaser in 1869. Stoichiometric as well as catalytic couplings utilising copper as transition metal are well established.¹

Over the course of our investigations concerning the cyclotrimerisation of alkynes and other [2+2+2] cycloadditions with low-valent cobalt catalysts² we applied 3-ethynylnitrobenzene in the cyclotrimerisation reaction (Scheme 1).



Scheme 1 Cobalt-catalysed Glaser coupling utilising a nitro-functionalised alkyne

To our surprise, no cyclotrimerisation product 1a or 1b was obtained, but the 1,3-diyne 2 was isolated in moderate yield (38%). This result is extremely unusual since the Glaser-type coupling to afford product 2 is an overall oxidation process. In contrast to the classical Glaser coupling reaction, the cobalt-catalysed reaction was performed under reductive conditions (zinc powder). To investigate this coupling reaction in more detail, we separated the nitro- and the alkyne functionalities from each

other and performed the cobalt-catalysed Glaser-type coupling of phenylacetylene in the presence of nitrobenzene (Scheme 2). The reaction produced the diyne **3** (see experimental section) in excellent yield without any traces of the previously reported cyclotrimerisation product of type **1**.³ Therefore, the nitrobenzene efficiently prevented the cobalt catalyst from initiating the trimerisation reaction pathway. This can be tentatively explained by assuming that the nitro group occupies coordination sites at the cobalt centre. To further investigate this reaction, the components were varied and the results are summarised in Table 1.



Scheme 2 Cobalt-catalysed Glaser coupling utilising phenylacetylene in the presence of nitrobenzene

| Table 1 Cobalt-Catalysed Glaser Coupling of Phenylacetylene to | |
|--|--|
| Generate 3 | |

| Entry | CoBr ₂ | Zn | ZnI_2 | PhNO ₂ | Yield (%) ^a |
|-------|-------------------|----|---------|-------------------|------------------------|
| 1 | + | + | + | + | 99 |
| 2 | + | + | + | - | 0 |
| 3 | + | + | _ | + | 0 |
| 4 | + | - | + | + | 0 |
| 5 | _ | + | + | + | 0 |
| | | | | | |

^a Phenylacetylene (1.0 mmol), $CoBr_2$ (0.1 mmol), Zn (1.0 mmol), ZnI_2 (0.2 mmol), nitrobenzene (1 mmol), and MeCN (1 mL), 12 h, 80 °C.

Only when all components were present was the formation of the diyne **3** observed, which can be rationalised in the following way; the cobalt bromide is dissolved in acetonitrile and forms a complex with the solvent. The zinc iodide acts as Lewis acid to abstract the bromide ligands from the proposed $\text{CoBr}_2(\text{MeCN})_n$ to increase the Lewis acidity of the cobalt centre. Nitrobenzene as well as the alkyne displaces the acetonitrile as coordinating ligands.

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The alkynes coordinate to the cobalt centre either as a bis- η^2 alkyne **4** or a cobaltacycle **5** which is generated via a formal oxidative addition (Scheme 3).



Scheme 3 Proposed initial steps towards the cobalt-catalysed Glaser coupling utilising phenylacetylene in the presence of nitrobenzene

These assumptions become reasonable because the reaction can also be conducted with additional bidentate diimine and pyridine-imine ligands on the cobalt(II) centre (see below) and an octahedral coordination sphere is a prerequisite to accommodate these cobalt diimine type complexes. In a cobalt(I) complex, which adopts a trigonal bipyramidal coordination sphere, the starting materials and reagents can not be incorporated easily. Nevertheless, a low-valent cobalt(I) complex generated upon reduction with zinc powder might act as a reducing agent towards a coordinated nitrobenzene ligand, resulting in the identical intermediate **6** (see Scheme 4).

The formation of **3** from the cobaltacycle **5** seems unlikely, because the two hydrogen atoms, which must be removed, are coplanar with the cobalt centre so that β hydride elimination can be excluded as the oxidation pathway. Therefore, we further propose that the Glaser-type oxidation process of the coordinated starting materials is initiated by an electron transfer from zinc powder to the activated nitrobenzene coordinated to the Lewis acidic cobalt centre in 4 (Scheme 4). This one electron reduction generates a radical type intermediate 6, which could act as a strong oxidising agent to initiate a net H-shift to form 7. Another net H-shift could result in the formation of water and the cobalt intermediate 8 where the two alkynes are σ bonded to the cobalt. A reductive elimination would then generate the product 3 and a cobalt nitrosobenzene complex.

In a separate experiment nitrosobenzene also proved to be active as an oxidising agent in this unprecedented Glaser-type coupling reaction. Nevertheless, the replacement of nitrobenzene by nitrosobenzene does give the coupling product **3**, but small amounts (5-10%) of the cyclotrimerisation products of type **1** are also detectable.

The cobalt-catalysed Glaser-type coupling was also achieved utilising a preformed cobalt complex with a N,N'-dicyclohexylethanediimine or triisopropyl phosphite ligand. In both cases the conversion of phenylacetylene with zinc powder led to the desired product **3** in 99% yields, whereas when tetra-*n*-butylammonium borohydride was used as the reducing agent no product was de-



Scheme 4 Proposed initial steps towards the cobalt-catalysed Glaser coupling, utilising phenylacetylene in the presence of nitrobenzene

tected. This leads to the interpretation that the zinc powder undergoes a single electron reduction to initiate the process which the borohydride can not. The use of catalytic amounts of zinc powder (20 mol%) led only to a conversion of 23% indicating that at least one electron from zinc powder is needed to initiate the overall reaction. The reduction of nitro- via nitrosobenzene led to aniline and diazobenzene which were detected via GCMS. The oxidising agent nitrobenzene can be altered and use of other aromatic nitro compounds led to complete conversions such as $C_6D_5NO_2$ and 1-nitronaphthylene.⁴ When 4-nitrobenzaldehyde, 4-cyanonitrobenzene and 1,3-dinitrobenzene were used only small amounts of 3 were obtained (10-30%) and the use of nitromethane did not result in the formation of 3 at all. 4-Chloro- and 4-fluoronitrobenzene are as effective as nitrobenzene itself resulting in 76%, 71% and 73% conversion after 3.5 hours of reaction time, respectively. 4-Methyl- and 4-methoxynitrobenzene were inferior to nitrobenzene resulting only in 57% and 45% conversion after 3.5 hours of reaction time. This indicates that the redox potentials seem to be critical for the successful transformation and that electron-rich as well as very strongly electron-deficient nitrobenzene derivatives are less effective in this transformation. The amount of converted nitrobenzene was determined by GC analysis utilising decane as internal standard. Reproducibly, on a 2 mmol scale (alkyne and nitrobenzene) only 30% of the nitrobenzene was converted. The consumed amount of nitrobenzene is sufficient to account for all redox equivalents required for the quantitative conversion of the alkyne. When the total amount of nitrobenzene was reduced to substoichiometric quantities (0.5 equiv with respect to the alkyne) the conversion of the alkyne was incomplete and the cyclotrimerisation product of the alkyne of type 1a (Ar = Ph) was observed.

The alternative oxidation pathway involving H_2 generation can be excluded because MS measurements of the gas atmosphere over the reaction mixture after complete conversion of the alkyne in a sealed reaction vessel revealed that no hydrogen gas was generated.

All attempts to intercept possible alkyne radical type intermediates in a radical-based reaction pathway upon addition of further substrates such as terminal alkenes, malonates, cinnamyl chloride, diazo esters, bromoform, propargyl bromide, and acyl amides resulted either in the unchanged formation of the diyne **3** or in no conversion at all. Therefore, we came to the conclusion that no radical type alkyne intermediates are present free in solution, but are rather coordinated to the cobalt centre and lead to the product **3** by rapid reductive elimination from **8**.

The preparative application of the cobalt-catalysed Glaser-type coupling was investigated on some selected examples utilising representative terminal alkynes. The results of these transformations (Scheme 5) are summarised in Table 2.

Scheme 5 Attempted synthesis of symmetrical diynes

Table 2 Results of the Cobalt-Catalysed Glaser-Type Coupling of Various Alkynes



^a Alkyne (1.0 mmol), $CoBr_2$ (0.05 mmol), Zn (1.0 mmol), ZnI₂ (0.1 mmol), nitrobenzene (1 mmol), and MeCN (1 mL), 12 h, 80 °C.

While the cobalt-catalysed Glaser-type coupling of phenylacetylene as well as of 2-ethynylthiophene proceeded with excellent isolated yields, the results for alkenyl-, alkyl- and silyl-substituted alkynes are moderate to good utilising cobalt bromide in the absence of any additional ligands.

Finally, we briefly investigated the application of cobalt bromide and selected cobalt complexes in a coupling reaction utilising 5 mol% of the cobalt catalyst to afford symmetrical as well as unsymmetrical diynes (Scheme 6) utilising equimolar quantities of phenylacetylene and hex-1-yne. The results are summarised in Table $3.^{5}$

The ratios of the desired products were detected by GC and NMR integration of suitable signals. Surprisingly, instead of a statistical mixture of products the phenylacety-lene was coupled more efficiently than hex-1-yne in all entries. The highest ratio of the unsymmetrical product **10**



Scheme 6 Attempted synthesis of unsymmetrical 1,3-diynes

Table 3 Results of the Cobalt-Catalysed Glaser-Type Coupling

 Utilising Two Different Alkynes

| Entry | Ligand | Product ratio ^a 3/10/11 |
|-------|----------------------------------|------------------------------------|
| 1 | none | 1.00:0.47:0.08 |
| 2 | 2 P(O <i>i</i> -Pr) ₃ | 1.00:0.72:0.38 |
| 3 | dppe | 1.00:0.33:0.42 |
| 4 | | 1.00:0.50:0.11 |
| 5 | | 1.00:0.54:0.41 |
| 6 | | 1.00:0.50:0.65 |
| 7 | | 1.00:0.48:0.13 |

^a Average of GC and NMR integration after >95% of the phenylace-tylene had converted.

was obtained for the phosphite ligand system, whereas the diimine- and the pyridine imine-type ligands gave an almost constant ratio of **3** to **10**, while the amount of **11** varied significantly. Nevertheless, complete chemoselectivity was not expected in these reactions, but the influence of ligands on the ratios of products, especially of the phosphite ligands, which gave the highest ratio of the unsymmetrical product **10**, might be worth investigating in the future in more detail.

In summary we were able to demonstrate that nitrobenzene can be used as a stoichiometric oxidant in the cobaltcatalysed Glaser-type coupling of aromatic alkynes whereas acceptable yields could be obtained with alkenyl-, aliphatic, and silyl-substituted alkynes. The unprecedented reaction mechanism of an oxidative coupling reaction under formally reductive conditions (stoichiometric amounts of zinc powder) could be useful in future applications where oxidation sensitive functional groups might interfere with traditional reaction protocols.

1,4-Diphenylbuta-1,3-diyne (3); Typical Procedure

To a suspension of $CoBr_2$ (22 mg, 0.1 mmol, 5 mol%), Zn (131 mg, 2.0 mmol, 1.0 equiv) and ZnI₂ (64 mg, 0.2 mmol, 10 mol%) in MeCN (1.0 mL) were added nitrobenzene (246 mg, 206 μ L, 2.0 mmol, 1.0 equiv) and phenylacetylene (204 mg, 220 μ L, 2.0 mmol)

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under argon. The reaction mixture was stirred at 80 °C for 12 h. After the addition of $\text{Et}_2O(5.0 \text{ mL})$, the mixture was filtered over silica gel (eluent: pentane– Et_2O , 2:1). The volatiles were removed and the product was purified by column chromatography (SiO₂, pentane) affording the product **3** (200 mg, 0.99 mmol, 99%) as a colourless solid. The analytical data are consistent with those reported in the literature.^{1b}

References

(1) (a) Glaser, C. Ber. Dtsch Chem. Ges. 1869, 2, 422.
(b) Eglinton, G.; Galbraith, A. R. J. Chem. Soc. 1959, 889.
(c) Eglinton, G.; McCrae, W. Adv. Org. Chem. 1963, 4, 225.
(d) Hay, A. S. J. Org. Chem. 1962, 27, 3320. (e) Boldi, A. M.; Anthony, J.; Knobler, C. B.; Diederich, F. Angew. Chem., Int. Ed. Engl 1992, 31, 1240; Angew. Chem. 1992, 104, 1270. (f) Siemsen, P.; Livingston, R. C.; Diederich, F. Angew. Chem. Int. Ed. 2000, 39, 2632; Angew. Chem. 2000, 112, 2740.

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- Harms, K. Synthesis 2008, 75. (c) Hilt, G.; Paul, A.; Harms, K. J. Org. Chem. 2008, 73, 5187.
 (3) (a) Hilt, G.; Hess, W.; Vogler, T.; Hengst, C. J. Organomet. Chem. 2005, 690, 5170. (b) Hilt, G.; Vogler, T.; Hess, W.;
- Galbiati, F. *Chem. Commun.* 2005, 1474.(4) The use of deuterated nitrobenzene led to the corresponding aniline and diazobenzene side products without loss of any
- deuterium labeling.
 (5) For the Cadiot–Chodkiewicz coupling, see: (a) Cadiot, P.; Chodkiewicz, W. In *Chemistry of Acetylenes*; Viehe, H. G., Ed.; Marcel Dekker: New York, **1969**, 597. (b) Siemsen, P.; Felber, B. In *Handbook of C-H Transformations*, Vol. 1; Dyker, G., Ed.; **2005**, 53–62. (c) Siemsen, P.; Felber, B. In *Handbook of C-H Transformations*, Vol. 1; Dyker, G., Ed.; **2005**, 83–84. (d) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841.