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Coupling of Alkynyllithiums to 1,3-Diynes by Reaction with Dichlorobis(triphenylphosphine)nickel(II) in the Presence of Triphenylphosphine and Guanidine or Amidine Bases

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Summary: Reaction of alkynyllithiums with $NiCl_2(PPh_3)_2$ *and 2L [L =* PPh_3*, tetramethylguanidine, 1,8-diazabicyclo[5.4.0]undec-7-ene,* $ArN{=}C(Me)NMe_2$*, or* $ArN{=}C(NMe_2)NMe_2$*] at low temperatures in THF resulted in moderate to good yields of the homocoupled products, 1,3-diynes. Experiments on cross-coupling suggested that the 1,3-diynes are produced by reductive elimination from intermediate dialkynylnickel species.*

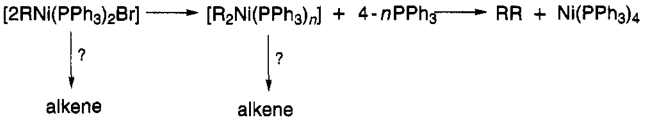
Introduction

During work on a new elimination of hydrogen halide from primary alkyl bromides and iodides to give terminal alkenes effected by oxidative addition of the halide to a nickel(0) reagent followed by β-hydride elimination,[1] a little (<10%) Wurtz-like coupling of the alkyl halide to a higher alkane was observed in some cases (notably those involving long-chain alkyl halides). This coupling was assumed to derive by reductive elimination from a dialkylnickel(II) complex[2] formed either as an intermediate in the elimination or in a side reaction from the initial alkylnickel halide (Scheme 1). The same reductive elimination had also been observed in the preparation of the tetrakis(triphenylphosphine)nickel(0) used as the reagent for this elimination. Thus, reaction of bis(triphenylphosphine)nickel(II) dichloride with 2 equiv of n-BuLi gave some n-octane (eq 1).

$$2\text{BuLi} + \text{NiCl}_2(\text{PPh}_3)_2 \xrightarrow{-2\text{LiCl}} [\text{Bu}_2\text{Ni}(\text{PPh}_3)_2] + 2\text{PPh}_3 \rightarrow \text{Bu}_2 + \text{Ni}(\text{PPh}_3)_4 \quad (1)$$

The coupling reaction should, of course, prevail over elimination in those substrates whose alkyl groups bear no β-hydrogens and may, indeed, become a useful reaction in those cases. Among such substrates are alkynes, and the reductive elimination in dialkynylnickel(II) species would provide a new, mild method to 1,3-diynes to add to the small, existing stock.[3] However, there are a couple of potential problems attending the use of these substrates. First, alkynes are easily trimerized to benzenes by nickel(0) phosphine complexes[4] including tetrakis(triphenylphosphine)nickel(0), the other product of the desired reductive elimination (fortunately, this does not appear to be true of 1,3-diynes[5]). Second, there were two earlier groups of reports on the preparation of dialkynylnickel(II)phosphine[6] and tetraalkynylnickel(II)ate[7] complexes which gave no indication of their propensity to undergo reductive elimination. The only previous example involving nickel in this sort of coupling required the reaction of alkynylnickeltricarbonyl complexes with iodine to effect the desired reductive elimination.[8] In contrast, the coupling of aryl, alkyl, and alkenyl groups by nickel catalysts is well-known.[9,10] Herein, we report on our investigation which shows that coupling of alkynyllithiums to 1,3-diynes by reductive elimination from nickel under stoichiometric conditions is indeed feasible.

Scheme 1



Results and Discussion

Of the two methods of preparing the requisite dialkynylnickel(II) species in solution, namely, oxidative addition of a 1-bromoalkyne to nickel(0) or substitution of halide on a nickel(II) halide by an alkynide anion, we chose the latter route as the more convenient in terms of availability of starting material (alkynide *versus* 1-haloalkyne) (Scheme 2), even though it meant the use of stoichiometric amounts of nickel.

The literature precedent mentioned above concerning their stability suggested that heat would be needed to decompose any intermediate dialkynylnickel species.

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Scheme 2

$$2RC{\equiv}CLi + NiCl_2(PPh_3)_2 \dashrightarrow [(RC{\equiv}C)_2Ni(PPh_3)_2] \dashrightarrow \underset{\textbf{1}}{RC{\equiv}CC{\equiv}CR} + Ni(PPh_3)_n$$

Table 1. Synthesis of Diynes 1

diyne	R	yield (%)
1b	*n*-C_5H_{11}	49
1c	*t*Bu	73
1d	$BnOCH_2CH_2$	31
1e	$THPO(CH_2)_2$	52
1f	$THPO(CH_2)_3$	51
1g	$THPO(CH_2)_4$	44

Accordingly, a solution of 2 equiv of phenylethynyllithium in tetrahydrofuran (THF) was added under anaerobic conditions to a suspension of $NiCl_2(PPh_3)_2$ in THF containing 2 equiv of triphenylphosphine under reflux. Heating was continued overnight and then the reaction was worked up by the addition of acid.

1,4-Diphenylbutadiyne (**1a**) was isolated after column chromatography in 38% yield. Before we attempted to optimize the yield of this reaction, we decided to check our assumption concerning the need for heat. Thus, the reaction was repeated at lower temperature (1.5 h at −78 °C, overnight at room temperature) with the addition of chlorotrimethylsilane (1.3 equiv) after the initial 1.5 h at −78 °C to act as a trap for any unreacted alkynyllithium. No (trimethylsilyl)phenylethyne was isolated after workup, indicating that transfer of alkynide from lithium to nickel had been complete (a control reaction established that the alkynyllithium was silylated quantitatively at −78 °C in the absence of nickel). To our surprise, **1a** was isolated in slightly better yield (45%) thereby showing that heat had, if anything, a somewhat deleterious effect. Since oxygen had been shown to induce reductive elimination from arylmethylnickel complexes,[9] a slightly modified version of these conditions was tested in which the reaction mixture was exposed to air after the initial phase. There was, however, no effect on the yield of the product. Under this more practicable version of conditions, a number of alkynes were coupled to give 1,3-diynes in moderate yields (Table 1). The best yield was obtained with the lithium derivative of *tert*-butylethyne (73%). Propargylic ethers were poor substrates, giving low yields and low recovery of starting material [6% diyne from $THPOC(Me)_2C{\equiv}CH$, <6% diyne from $THPOC(CH_2)_5C{\equiv}CH$]; trimethylsilylethyne and 1,7-octadiyne reacted but failed to give the desired products. In each successful reaction, the product was accompanied by varying quantities of oligomers (e.g., 57% combined yield from $PhC{\equiv}CLi$ after heating) as detected by mass spectrometry on fractions obtained by column chromatography. The exact nature of these oligomers was not ascertained, but mass ions corresponding to species up to heptameric were detected. We believe that they result from interaction of an alkynic species with the nickel(0) generated in the final reductive elimination. However, they do not appear to derive substantially from the product diynes; a control reaction in which 1,4-diphenylbutadiyne was subjected to nickel(0) under the conditions of the coupling reaction resulted in 80% recovery of the diyne. The missing 20% is insufficient to account for the total amount of oligomers formed in the coupling reactions. The low yield of oligomers from *tert*-butylethyne may reflect a steric inhibition of oligomerization. Such an effect has been observed by us in the cocyclization of diynes and monoynes.[11]

Table 2. Influence of the Ligand on the Yields of Products from the Coupling Reaction of 1-Lithio-4-benzyloxybutyne

ligand	starting material (%)	diyne **1d** (%)	oligomers (%)
PPh_3	12	31	<9
TMG	36	42	8
2a	13	34	42
2b	30	40	nd[a]
2c	16	29	nd[a]
DBU	26	29	nd[a]
3a	13	38	18
3b	19	24	29
3c	32	19	30

[a] nd, not determined.

Attempts to find conditions in which the competing oligomerization was reduced to a minimum focused on the lithium species of phenylethyne and 4-(benzyloxy)-butyne. Our belief that nickel(0) was the mediator of oligomerization prompted the addition of *tert*-butyl bromide (2.55 equiv), which should trap the low-valent metal by oxidative addition. Indeed, its presence increased the yield of **1a**, albeit slightly (52%). Attempts to remove nickel(0) by the addition of a mild oxidizing agent such as trimethylamine *N*-oxide, triphenylphosphine oxide, or iodine led to lower yields ($Me_3NO{\cdot}2H_2O$, 23% at −100 °C; PPh_3PO, 19% at −78 °C; I_2, 27% at −78 °C).

The nitrogenous ligands, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and tetramethylguanidine (TMG), had been used to good effect in suppressing side reactions in the earlier β-elimination reaction.[1] These were, therefore, added in separate experiments in place of the extra 2 equiv of triphenylphosphine. The amidine, DBU, effected a slight improvement in the yield of **1a** (52%), but TMG was much better giving a 65% yield of 1,4-diphenylbutadiyne. The presence of the NH on TMG necessitated adding the base 5 min after the alkynide in order to avoid protonation of the latter. Likewise, the yield of 1,8-dibenzyloxyocta-3,5-diyne improved from 31% to 42%.

This remarkable effect of TMG prompted a study of the *N*-aryl derivatives **2**[12] of TMG, which we hoped would provide some indication of the electronic influence of the guanidine as a ligand and at the same time remove the problem of the "acidic" NH. For comparison purposes we also prepared the related amidines **3**.[13] With these bases the coupling of 4-benzyloxybutynyllithium was studied with respect to the recovery of the alkyne, the yield of the diyne and the yield of oligomers (Table 2). In each case the absence of silylated starting material as a product when the reaction was carried out in the presence of chlorotrimethylsilane indicated that alkynide transfer to nickel was complete. The substantial amounts of starting materials recovered presumably, therefore, derive from protonolysis of alkynylnickel species on workup. The amidines **3** show a small but steady progression, the yields of diyne dropping as the recovery of starting material and yields of oligomers

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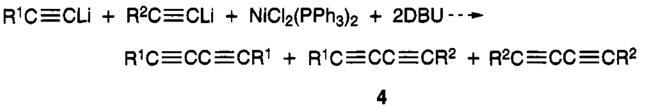
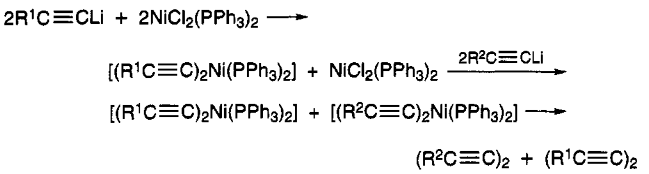
Scheme 3



$$R^1C{\equiv}CLi + R^2C{\equiv}CLi + NiCl_2(PPh_3)_2 + 2DBU \dashrightarrow R^1C{\equiv}CC{\equiv}CR^1 + \underset{4}{R^1C{\equiv}CC{\equiv}CR^2} + R^2C{\equiv}CC{\equiv}CR^2$$

Scheme 4



$$2R^1C{\equiv}CLi + 2NiCl_2(PPh_3)_2 \longrightarrow [(R^1C{\equiv}C)_2Ni(PPh_3)_2] + NiCl_2(PPh_3)_2 \xrightarrow{2R^2C{\equiv}CLi} [(R^1C{\equiv}C)_2Ni(PPh_3)_2] + [(R^2C{\equiv}C)_2Ni(PPh_3)_2] \longrightarrow (R^2C{\equiv}C)_2 + (R^1C{\equiv}C)_2$$

increase with increasing electron-withdrawing power of the aryl substituent. The guanidines **2** are more evenly balanced with none of them providing a substantial synthetic benefit over that obtained with TMG itself. There is not much to choose between the best amidine [p-MeOC$_6$H$_4$N=C(Me)NMe$_2$] (38%), the best guanidine [PhN=C(NMe$_2$)NMe$_2$] (40%), and TMG (42%), leaving uncertain a decision concerning their mode of interaction with nickel during the critical reductive elimination step, if any. Whatever the exact mechanistic details of the mode of action of TMG and related bases are, it is clear that their presence generally helps to reduce the extent of oligomer production, and in the case of TMG, allowing for the recovery of starting material, yields are enhanced.

The use of the bidentate phosphorus ligand 1,2-bis(diphenylphosphino)ethane gave no enhancement of yield (32%) within experimental error compared to triphenylphosphine (31%) and the nitrogenous bidentate ligands, tetramethylethylenediamine and 2,2′-bipyridyl, blocked diyne formation completely.

Finally, of some potential significance both mechanistically and synthetically is whether the reaction can be used for the cross-coupling of alkynes. Three combinations of alkynes were tried, namely, phenylethyne and 4-(benzyloxy)but-1-yne, 6-(tetrahydropyranyloxy)hex-1-yne and *tert*-butylethyne, 4-(tetrahydropyranyloxy)but-1-yne, and 1-heptyne. In each case, the homocoupled products **1** dominated (Scheme 3) (in the first case very little difference in the product distribution was observed by reversing the order of addition of the two alkynyllithiums).

Some cross-coupled diynes **4** were obtained but not in synthetically significant amounts. However, the results are informative mechanistically. The fact that a far from statistical distribution of diynes was obtained argues against the predominant formation of these products by free alkynic species such as radicals and is suggestive of a role for nickel in the reaction, i.e., reductive elimination (in the absence of nickel no coupling occurs). This conclusion is supported by the absence of influence of oxygen in the homocoupling reaction. The preponderance of homocoupled products suggests that reductive elimination occurs from a dialkynylnickel and that this intermediate was formed by displacement of both chloride ligands from NiCl$_2$(PPh$_3$)$_2$ at approximately the same rate (Scheme 4). Disproportionation between various alkynylnickel chlorides as a route to the dialkynylnickel is not indicated since this should give more cross-coupled product. Likewise, reductive elimination from a mixed tri- or tetraalkynylnickelate is unlikely for the same reason.

Conclusion

Notwithstanding a mechanism which militates against a potentially useful cross-coupling process, we have demonstrated that the homocoupling of alkynides by interaction with nickel(II) is productive.

Experimental Section

Melting points were determined on a Kofler hot stage or Gallenkamp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 881 grating spectrophotometer as thin films or Nujol mulls unless otherwise stated; the type and intensity of signal is denoted as follows: very strong (vs), strong (s), medium (m), weak (w), and broad (br). ^{1}H and ^{13}C NMR spectra were recorded on JEOL FX 90Q, Bruker WM-250, JEOL GSQ 270, and Bruker AM-500 spectrometers in chloroform-*d* with tetramethylsilane or residual chloroform as internal standards. Signals are quoted as singlet (s), triplet (t), multiplet (m), and broad (br). Mass spectra were recorded on a VG Micromass 7070B machine by the EI method.

Starting Materials. Preparative gravity column chromatography was performed on Crosfield Sorbsil C60 silica gel. Petroleum refers to light petroleum of bp 40–60 °C. Ether refers to diethyl ether. Ether and THF were distilled from sodium/benzophenone and potassium metal, respectively, under argon just prior to use. Dichloromethane was distilled from phosphorus pentoxide. Butyllithium was purchased from Aldrich Chemicals as solutions in hexanes. All other solvents and reagents were purified by standard methods. Anhydrous NiCl$_2$ was prepared by heating the hexahydrate to 180 °C until it changed to an orange color (generally for 2 days) and then cooling under argon.

General Procedure for the Homocoupling of Alkynes. To a stirred solution of alkyne (1 equiv) in dry THF under argon at room temperature was added butyllithium solution (1.6 mol dm^{-3}, 1 equiv) to generate the alkynyllithium. This was cooled to −78 °C and added to a stirred suspension of anhydrous NiCl$_2$ (0.5 equiv) and triphenylphosphine (2 equiv) in dry THF under argon at −78 °C. The reaction mixture was allowed to warm to room temperature over 1.5 h and then stirred for a further 2 h. The reaction flask was then opened to the atmosphere, and the mixture was left to stir overnight. Petroleum (100 mL) and iodomethane (5 mL, to remove PPh$_3$) were added, and after 3 h the mixture was filtered. The filtrate was rotary evaporated and the residue purified by distillation or column chromatography. The following are illustrative of 1,3-diynes which can be made. Other examples are provided in the supplementary material.

2,2,7,7-Tetramethylocta-3,5-diyne (1c): from *tert*-butylethyne (4 mmol) as a white solid (240 mg, 73%); mp 128–9 °C (Lit.[14] mp 130–1 °C), eluted from silica gel using petroleum; ^{1}H NMR (90 MHz) $^\delta$H 1.2 (18 H, s, Me); ^{13}C (23.5 MHz) $^\delta$C 28, 31, 64 (*C*C*C*C), 86 (C*C*C*C*); MS *m/z* 162 (M$^+$, 100%), 147 (M$^+$ − Me, 43%), 105 (M$^+$ − *t*Bu, 43%).

1,8-Dibenzyloxyocta-3,5-diyne (1d): from 4-(benzyloxy)but-1-yne (0.9 mmol) as a white solid (44 mg,

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31%); mp 39 °C. Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96%. Found: C, 82.67; H, 6.99. HRMS Calcd for $C_{22}H_{21}O_2$: $M^+ - H$, 317.1542. Found: $M^+ - H$, 317.1543. ^1H NMR (270 MHz) $^{\delta}H$ 2.6 (4 H, t, *J* 6.8 Hz, 2 propargylic CH_2), 3.6 (4 H, t, *J* 6.8 Hz, 2 CH_2O), 4.55 (4 H, s, 2 benzylic CH_2), 7.35 (10 H, s, 2 Ph); ^{13}C NMR (23.5 MHz) $^{\delta}C$ 21 (propargylic CH_2), 68 (CH_2O), 66 (*C*CCC), 73 (benzylic CH_2), 74 (C*C*CC), 128, 128.5, 138; MS *m/z* 318 (M^+, 0.1%), 317 ($M^+ - H$, 0.2%), 107 ($PhCH_2O^+$, 20%), 91 ($PhCH_2^+$, 100%).

Homocoupling of Phenylethyne in the Presence of TMG. To a stirred solution of phenylethyne (186 mg, 1.82 mmol) in dry THF (15 mL) under argon at room temperature was added butyllithium solution (1.6 mol dm^{-3}, 1.1 mL, 1.76 mmol). After 30 min, the alkynide solution thus generated was cooled to −78 °C and added to a suspension of $NiCl_2(PPh_3)_2$ (600 mg, 0.92 mmol) in dry THF (20 mL) at −78 °C. After 5 min at this temperature, tetramethylguanidine (280 mg, 2.4 mmol) was added over 2 min. The reaction mixture was stirred for a further 55 min and then treated with chlorotrimethylsilane (0.5 mL, 3.9 mmol). After 30 min, the reaction mixture was exposed to air, allowed to warm to room temperature over 1 h, and treated with 2 M hydrochloric acid (5 mL). The mixture was taken up in ether (100 mL), the layers were separated, and the aqueous layer was extracted with a further portion of ether (30 mL). The combined ethereal layers were washed successively with saturated sodium bicarbonate solution until no longer acid, water until neutral, and brine (1×) and then dried ($MgSO_4$). The drying agent was filtered and the filtrate rotary evaporated to dryness. The residue was dissolved in petroleum (150 mL) and stirred with iodomethane (2 mL, to remove PPh_3) for 3 h. The mixture was filtered, the filtrate was evaporated, and the residue was chromatographed on silica gel using petroleum as eluent to give 1,4-diphenylbutadiyne as a white solid (120 mg, 65%): mp 86−8 °C (Lit.[14] mp 88 °C); IR (cm^{-1}) 1594 (m), 1486 (s), 1439 (s), 755 (vs), 687 (vs); ^1H NMR (90 MHz) $^{\delta}H$ 7.2−7.6 (10 H, m, Ar); ^{13}C NMR (23.5 MHz) $^{\delta}C$ 71, 85, 122, 128, 129, 132.5; MS *m/z* 202 (M^+, 49%), 178 ($M^+ - 2C$, 100%).

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Supplementary Material Available: Synthesis and analytical data for **1a**, **1b**, **1e**−**h**, **4a**, **4b**, and **5** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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