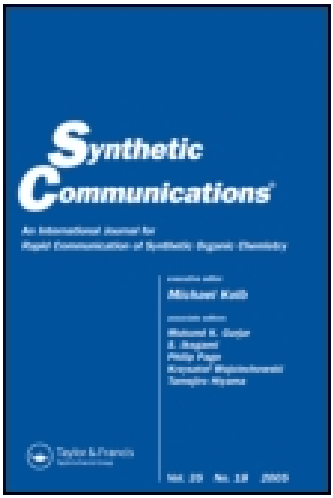

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Homocoupling of Halotropones Promoted by Bis(1,5-cyclooctadiene) Nickel in the Presence of Tris(1-pyrazolyl)methane: An Easy Route to [Bi-1,3,5-cycloheptatrien-1-yl]-7,7′-diones

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Homocoupling of Halotropones Promoted by *Bis*(1,5-cyclooctadiene) Nickel in the Presence of *Tris*(1-pyrazolyl)methane: An Easy Route to [Bi-1,3,5-cycloheptatrien-1-yl]-7,7′-diones

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Abstract: An efficient homocoupling of 2-halotropones, to afford 2,2′-bitropones, occurs in toluene at rt in the presence of stoichiometric amounts of $[Ni(cod)_2]$ and *tris*(1-pyrazolyl)methane ligand, in a 1:1 molar ratio. This methodology was extended to aryl halides.

Keywords: Halotropones, homocoupling, nickel, *tris*(pyrazolyl)methane

INTRODUCTION

Direct coupling of aryl halides under catalysis by zero-valent nickel reagents is known to provide an effective entry to symmetric biaryls under mild conditions with high yield. The original Semmelhack's conditions,[1] which require stoichiometric amounts of expensive and air-sensitive *bis*(1,5-cyclooctadiene) nickel ($[Ni(cod)_2]$) in dimethylformamide (DMF), were repeatedly modified and improved in the ensuing 37 years.[2] Importantly, the active nickel(0) complex was prepared in situ from air-stable complexes,[3–7] or salts,[8–12] both in stoichiometric[3,5] and catalytic amounts,[4,6,7,10–12] via chemical (Zn[3–7,9,10] or other metals[8,10–12]) or electrochemical reduction[13,14] in the presence of triphenylposphine and/or an appropriate ligand.[10,15,16]

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Homocoupling of a few types of aryl halides was thus notably improved, but limitations remain for other classes of organic halides. For example, with 2-, 3-, and 4-halotropones, which are prone to give organometallic compounds in the presence of reducing metals, all modifications to Semmelhack's recipe give extremely poor yields. This is because the organotropone that is formed undergoes further reaction with unreacted halotropone, leading to a complex mixture of products. It is well known, for example, that Grignard reagents with 2-chlorotropone mostly give ring-contraction products or products of C-7 addition.[17] Thus 2-, 3-, and 4-chloro- and bromotropone at 50°C for 3 h in the presence of a catalytic amount of Ni(0) formed in situ by reduction of $[NiBr_2(PPh_3)_2]$ with active Zn in the presence of Et_4NI in benzene gave 2,2′-, 3,3′-, and 4,4′-bitropones, respectively, in poor yields, while the bulk of the reagents remained unreacted.[6] Prolonged reaction times caused a further decrease in the yields.[6] With samarium,[12] which is reported to tolerate a variety of functional groups and give high yields under mild conditions, 2-chlorotropone led to only traces of homocoupling product in our hands (see Experimental, method C).

This article deals with the stoichiometric homocoupling of 2-halotropones and aryl halide promoted by $[Ni(cod)_2]$ in the presence of the *tris*(1-pyrazolyl)methane (TPM) ligand.

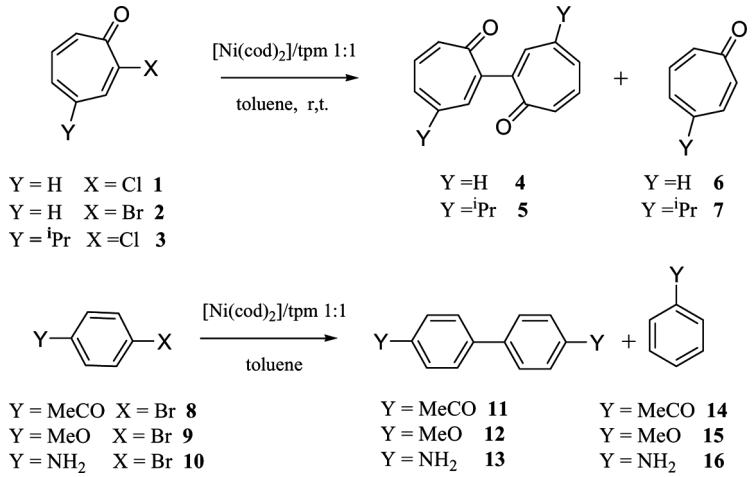
RESULTS AND DISCUSSION

Because the presence of the reducing metal for the active Ni(0) species in situ production is detrimental for homocoupling of halotropones, we turned to the original Semmelhack conditions.[1] Starting with 2-chlorotropone (**1**), 2-bromotropone (**2**), and 2-chloro-4-isopropyltropone (**3**), moderate yields of homocoupled products were obtained, along with appreciable amounts of reduction products (Table 1 and Experimental).

Table 1. $[Ni(cod)_2]$-catalyzed homocoupling of halotropones in DMF (Semmelhack's conditions)

Substrate	Reaction time (h)	Temperature (°C)	Product and coupling yield (%)[a]	Product and reduction yield (%)[a]
1	2	20	**4**, 57	**6**, 23
2	2	20	**4**, 69	**6**, 24
3	2	20	**5**, 50	**7**, 12

[a]From HPLC analysis.



Scheme 1. [Ni(cod)$_2$]/TPM-catalyzed homocoupling of halotropones and aryl halides in toluene.

To minimize reductive processes, improve the yields of homocoupled products, and simplify the recovery, we devised a new method. As shown in Scheme 1, halotropones **1** and **2** gave [bi-1,3,5-cycloheptatrien-1-yl]-7,7′-dione (2,2′-bitropone) (**4**) and tropone (**6**), wereas **3** led to [bi-3-isopropyl-1,3,5-cycloheptatrien-1-yl]-7,7′-dione (**5**) and 4-isopropyltropone (**7**).[18] The methodology involved adding the halotropone to a stirred slurry in toluene of a neutral tridentate ligand binding transition metal such as TPM[19] and [Ni(cod)$_2$] in molar ratio 1.54:1:1 at rt under argon.

Monitoring by high-performance liquid chromatography (HPLC) gave a clue as to the reaction course. Evaporation of the mixture at reduced pressure furnished a residue that was subjected to silica-gel thin-layer chromatography (TLC) to give cleanly the coupling product. Reaction times and yields of both homocoupling products and reduction products are given in Table 2.

On increasing the TPM/[Ni(cod)$_2$] molar ratio from 1 to 1.5, the yields of both **4** and **5** dropped by half.

Attempts to make the Ni(cod)$_2$/TPM homocoupling of **2** using samarium as reducing metal catalytic resulted in the disappearance of the starting material, and only traces of both **4** and **6** were found (see Experimental, method B).

Our methodology was also applied to typical, and frequently investigated, aryl halides, such as *p*-bromoacetophenone (**8**), *p*-bromoanisole (**9**), and *p*-bromoaniline (**10**) (Scheme 1). With **8**, which is activated by electron-withdrawing MeCO in the *p*-position, the homocoupling ran

Table 2. [Ni(cod)$_2$]/TPM-catalyzed homocoupling of halotropones and aryl halides in toluene

Substrate	Reaction time (h)	Temperature (°C)	Product and coupling yield (%)	Product and reduction yield (%)
1	2.5	20	**4**, 77[a]	**6**, 8[a]
2	1.5	20	**4**, 81[a]	**6**, 5[a]
3	2.0	20	**5**, 75[a]	**7**, 5[a]
8	6.0	20	**11**, 80[a]	**14**, 0[a]
9	8.0	20	**12**, 74[b]	**15**, 26[b]
10	2.0	50	**13**, 56[b]	**16**, 44[b]

[a]Isolated yield.
[b]From HPLC analysis.

smoothly, giving biaryl **11** in practically quantitative yield in 6 h at rt (Table 2). This represents a marked improvement on Semmelhack's methodology,[1] where temperatures are higher (45°C) and reaction times longer (36 h). With substrates carrying electron-donating substituents in the *p*-position, such as **9** and **10**, we obtained contradictory results. The bromocompound **9**, under our reaction conditions, behaved like those previously observed,[1,10] whereas **10** reacted slowly and mainly along the competitive reduction route to give aniline.[20]

The mechanism of these coupling reactions is under investigation. We reckon that TPM works as an auxiliary ligand, but its behavior seems to differ from 2,2′-bipyridine and its derivatives.[16] In fact, ^{1}H NMR spectra ruled out any ligand exchange reactions of [Ni(cod)$_2$] with TPM. Interaction of the TPM ligand probably occurs with a Ni(II) intermediate species arising from the initial process of oxidative addition[10] of the organic halide to Ni(0). Whatever is its exact role in the reaction mechanism, TPM makes it possible to use a scarcely polar solvent such as toluene. We recall that the *only* solvent that has been found to be satisfactory for the original Semmelhack coupling reaction is DMF.[1] Competitive coordination by a reagent such as **10** would lead to low yields of homocoupling product.

CONCLUSIONS

In spite of some limitations, our methodology provides simple and efficient entries to 2,2′-bitropones. It is now feasible to assay the biological activity of these substrates under fair prospects, given the remarkable biological activity of the cycloheptatrienone nucleus.[21] If so, the use of expensive [Ni(cod)$_2$] in stoichiometric amounts would be justified.

EXPERIMENTAL

General Remarks

Toluene (C. Erba) was distilled from Na under an atmosphere of Ar. DMF (C. Erba) was distilled from CaO and stored over 30-μm molecular sieves under an atmosphere of Ar. [Ni(cod)$_2$] (Aldrich) was used as such. TPM was prepared according to literature.[19] Halotropones[22] **1** and **2** and 2-chloro-4-isopropyltropone[23] (**3**) were prepared as previously reported. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 200-MHz spectrometer. All chemical shifts were reported in δ units with reference to TMS (^{1}H) or the signals of the solvent (^{13}C). UV-visible spectra were recorded on Hitachi 200 Perkin-Elmer spectrophotometer. HPLC analyses were performed with a Jasco Bip-1 pump equipped with a Jasco Uvidec-100-V spectrophotometer.

Homocoupling of Halotropones and Aryl Halides in Toluene Promoted by *Bis*(1,5-cyclooctadiene) Nickel in the Presence of TPM

[Bi-3-isopropyl-1,3,5-cycloheptatrien-1-yl]-7,7′-dione (**5**)

TPM (0.047 g, 0.219 mmol) was added under Ar to a stirred solution of [Ni(cod)$_2$] (0.060 g, 0.218 mmol) in toluene (6.5 mL). Compound **3** (0.061 g, 0.337 mmol) was added to the slurry, and the resulting mixture was stirred at rt for 2 h. Evaporation at reduced pressure of the reaction mixture led to a residue that was subjected to silica-gel TLC (Et_2O, $R_f = 0.33$) to give [bi-3-isopropyl-1,3,5-cycloheptatrien-1-yl]-7,7′-dione **(5)** 0.037 g (0.126 mmol, 75% yield) as a colorless solid (mp 145°C) and 4-isopropyltropone (**7**) (nezukone)[18] ($R_f = 0.5$) (0.0025 g, 0.017 mmol, 5% yield).

Data for **5**: Mp 145°C (dec); UV (EtOH) λ_{max} (log ϵ) 310 (4), 237 (4.3) nm; ^{1}H NMR [200 MHz, $(CD_3)_2CO$], δ 1.28 (d, $J = 7.0$ Hz, 6H), 2.90 (heptet, $J = 7.0$ Hz, 1H), 6.84 (dd, $J = 12.2$ Hz, $J = 1.2$ Hz, 1H), 6.96 (ddd, $J = 7.60$ Hz, $J = 1.8$ Hz, $J = 1.2$ Hz, 1H), 7.19 (dd, $J = 12.2$ Hz, $J = 7.60$ Hz, 1H), 7.35 (d, $J = 1.2$ Hz, 1H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.4, 38.5, 129.7, 136.2, 137.7, 139.6, 154.9, 185.2. HRMS: found M^+ 294.16186 (0.00012): $C_{20}H_{22}O_2$ requires 294.16198.

[Bi-1,3,5-cycloheptatrien-1-yl]-7,7′-dione (**4**)

Compound **4** was prepared as described for the previous compound starting from **1** (0.042 g, 0.300 mmol) TPM (0.042 g, 0.195 mmol), and [Ni(cod)$_2$] (0.053 g, 0.194 mmol). We obtained 0.024 g of bitropone **4**

(0.115 mmol, 77% yield) and 0.0025 g of tropone **6** (0.024 mmol, 8% yield). When starting from **2** (0.055 g, 0.300 mmol), TPM (0.042 g, 0.195 mmol), and [Ni(cod)$_2$] (0.053 g, 0.194 mmol), we recovered 0.0255 g of bitropone **4** (0.121 mmol, 81% yield) and 0.0016 g of tropone **6** (0.015 mmol, 5% yield). Analytical data agreed with the literature.[6]

4,4′-Diacetylbiphenyl (**11**)

Compound **11** was prepared as described for the troponoids starting from p-bromoacetophenone (**8**) (0.069 g, 0.35 mmol), TPM (0.053 g, 0.25 mmol), and [Ni(cod)$_2$] (0.064 g, 0.24 mmol) in 5 ml of toluene. After 6 h at rt, evaporation at reduced pressure of the reaction mixture led to a residue that was subjected to silica-gel TLC (hexane/AcOEt 80:20, $R_f = 0.27$) to give **11** (0.033 g, 0.14 mmol, 80% yield). Data for **11** agreed with those of a commercial (Aldrich) sample.

4,4′-Dimethoxy-1,1′-biphenyl (**12**)

Compound **12** was prepared as described for **11** starting from p-bromoanisole (**9**) (0.0445 g, 0.24 mmol), TPM (0.036 g, 0.17 mmol), and [Ni(cod)$_2$] (0.046 g, 0.17 mmol) in 3.5 ml toluene. After 8 h at rt HPLC analysis [250-mm column Si 60, eluent n-hexane/$(CH_3)_2$CHOH 0.2%, using standard solution of **12** and **15** (commercial Aldrich products)] gave 76 and 26% yields for **12** and **15** respectively.

Benzidine (**13**)

Compound **13** was prepared starting from 4-bromoaniline (**10**) (0.035 g, 0.20 mmol), TPM (0.031 g, 0.145 mmol), and [Ni(cod)$_2$] (0.039 g, 0.142 mmol). After stirring for 2 h at 50°C, HPLC analysis [250 mm column Lichrosorb CN, eluent n-hexane/EtOAc 50:50 using standard solutions of commercial available (Aldrich) **13** and **16**] gave 56 and 44% yields for **13** and **16** respectively.

Homocoupling of Halotropones and Aryl Halides Promoted by *Bis*(1,5-cyclooctadiene) Nickel in DMF (Semmelhack's Methodology)[1]

Bi-1,3,5-cycloheptatrien-1-yl]-7,7′-dione (**4**) and [Bi-3-isopropyl-1,3,5-cycloheptatrien-1-yl]-7,7′-dione (**5**)

DMF solutions of halotropones **1**, **2**, and **3** 0.05 M and [Ni(cod)$_2$] 0.03 M were prepared and stirred under Ar for 2 h at rt The yields of the

reactions were determined by HPLC analysis (250-mm column Lichrosorb CN, eluent EtOAc) using standard solutions of **4**, **5**, **6**, and **7**.

From **1** and **2**, we obtained **4** in 57 and 69% yields and **6** in 23 and 24% yields, respectively, whereas **3** gave **5** in 50% yield and **7** in 12% yield.

Homocoupling of Halotropones Promoted by Ni(0) in Catalytic Amounts

Method A

Compound **1** (0.085 g, 0.605 mmol) was dissolved under Ar in DMF (8.5 mL) containing Zn (0.075 g, 1.15 mmol), $(C_6H_5)_3P$ (0.080 g, 0.305 mmol), and $[Ni(cod)_2]$ (0.0085 g, 0.030 mmol). The mixture was stirred at rt, and the reaction was monitored with HPLC (250-mm column Lichrosorb CN, eluent EtOAc) using standard solution of **4** and **6**. After 4 days, ca. 70% of troponoid disappeared and only traces of bitropone were detected.

Method B

Compound **1** (0.072 g, 0.513 mmol) was dissolved under Ar in DMF (7.2 mL) containing Sm (0.129 g, 0.858 mmol), TPM (0.029 g, 0.135 mmol), and $[Ni(cod)_2]$ (0.0072 g, 0.026 mmol). The mixture was stirred at rt, and the reaction was monitored with HPLC as before. After 20 h, the reaction was complete, and only traces of both **4** and **6** were found.

Method C

Compound **1** (0.072 g, 0.513 mmol) was dissolved under Ar in DMF (7.2 mL) containing Sm (0.137 g, 0.911 mmol), $(C_6H_5)_3P$ (0.076 g, 0.289 mmol), and $[Ni(cod)_2]$ (0.0076 g, 0.028 mmol). The mixture was stirred at rt, and the reaction monitored with HPLC as before. After 20 h, the reaction was complete, and only traces of both **4** and **6** were found.

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REFERENCES

1. Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. Synthesis with zerovalent nickel: Coupling of aryl halides with bis(1,5-cyclooctadiene) nickel(0). *J. Am. Chem. Soc.* **1971**, *93*, 5908–5910.
2. Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Aryl-aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **2002**, *102*, 1359–1469.
3. Kende, A. S.; Liebeskind, L. S.; Braitsch, D. M. In situ generation of a solvated zero-valent nickel reagent: Biaryl formation. *Tetrahedron Lett.* **1975**, 3375–3378.
4. Zembayashi, M.; Tamao, K.; Yoshida, J.-I; Kumada, M. Nickel-phosphine complex–catalyzed homo coupling of aryl halides in the presence of zinc powder. *Tetrahedron Lett.* **1977**, 4089–4092.
5. Howarth, J.; James, P.; Dai, J. The coupling of aryl halides in the ionic liquid [bmim]PF6. *Tetrahedron Lett.* **2000**, *41*, 10319–10321.
6. Iyoda, M.; Sato, K.; Oda, M. A. Simple synthesis of bitropones and conversion of 2,2′-bitropone into dicyclohepta[*b,d*]furan dication, a novel dication species. *Chem. Commun.* **1985**, 1547.
7. Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. Homocoupling of aryl halides using nickel(II) complex and zinc in the presence of Et_4NI: An efficient method for the synthesis of biaryls and bipyridines. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 80–87.
8. Alonso, F.; Riente, P.; Yus, M. Homocoupling of aryl iodides promoted by nickel(0) nanoparticles. *Arkivoc* **2008**, *4*, 8–15.
9. Tao, X.-C.; Zhou, W.; Zhang, Y.-P.; Dai, C.-Y.; Shen, D.; Huang, M. Homocoupling of aryl bromides catalyzed by nickel chloride in pyridine. *Chin. J. Chem.* **2006**, *24*, 939–942.
10. Colon, I.; Kelsey, D. R. Coupling of aryl chlorides by nickel and reducing metals. *J. Org. Chem.* **1986**, *51*, 2627–2637.
11. Chen, C. $NiCl_2/CrCl_2$/Mn-mediated homocoupling of aryl halides accomplished in the presence of bipyridyl-type ligand. *Synlett* **2000**, 1490–1492.
12. Zheng, X.; Zhang, Y. Coupling reaction of aryl halides promoted by $NiCl_2/PPh_3/Sm^0$. *J. Chem. Res.* **2002**, 562–563.
13. Raynal, F.; Barhdadi, R.; Perichon, J.; Savall, A.; Troupel, M. Water as solvent for nickel-2,2′-bipirydine-catalysed electrosynthesis of biaryls from haloaryls. *Adv. Synth. Catal.* **2002**, *344*, 45–49.
14. Barhdadi, R.; Courtinard, C.; Nédélec, J. Y.; Troupel, M. Room-temperature ionic liquids as new solvents for organic electrosynthesis: The first examples of direct or nickel-catalysed electroreductive coupling involving organic halides. *Chem. Comm.* **2003**, 1434–1435.
15. Yamamoto, T.; Wakabayashi, S.; Osakada, K. Mechanism of C-C coupling reactions of aromatic halides, promoted by $Ni(COD)_2$ in the presence of 2,2′-bipyridine and PPh_3, to give biaryls. *J. Organomet. Chem.* **1992**, *428*, 223–237.
16. Abla, M.; Yamamoto, T. Kinetic study of ligand exchange reactions of bis(1,5-cyclooctadiene) nickel(0) with 2,2′-bipyridine, 4,4′-dimethyl-2,2′-bipyridine, and 4,4′,5,5′-tetramethyl-2,2′-bipyridine. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 1255–1261.

17. Cavazza, M.; Morganti, G.; Pietra, F. Reactions of 2-fluorotropone with Grignard reagents. *J. Chem. Soc.* **1984**, 724–728.
18. Cavazza, M.; Guerriero, A.; Pietra, F. A photochemical route to 4-alkyltropones including nezukone. *J. Chem. Soc. Perkin Trans. 1* **1986**, 2005–2008.
19. Reger, D. L.; Grattan, T. C.; Brown, K. J.; Little, C. A.; Lamba, J. J. S.; Rheingold, A. L.; Sommer, R. D. Syntheses of tris(pyrazolyl)methane ligands and {[tris(pyrazolyl)methane]$Mn(CO)_3$}SO_3CF_3 complexes: Comparison of ligand donor properties. *J. Organomet. Chem.* **2000**, *607*, 120–128.
20. TPM itself can act as an active hydrogen source to produce reduction products. The methynic proton of the TPM ligand in Ru(II) complexes is not observed in ^1H NMR spectra because of a fast exchange with D_2O (Llobet, A.; Doppelt, P.; Meyer, T. J. Redox properties of aqua complex of ruthenium(II) containing the tridentate ligands 2,2':6',2''-terpirydine and tris (1-pyrazolyl)methane. *Inorg. Chem.* **1988**, *27*, 514–520). Moreover the metallation at one of the pyrazole ring carbon atom of TPM complexes, affording a hydride complex, was observed (Heinekey, D. M.; Oldham, W. J.; Wiley, J. S. Cyclometalation of a pyrazolyl arm in hydridotris(1-pyrazolyl)borate and tris(1-pyrazolyl)methane complexes of iridium. *J. Am. Chem. Soc.* **1996**, *118*, 12842–12843).
21. Matsumura, E.; Morita, Y.; Date, T.; Tsujibo, H.; Yasuda, M.; Okabe, T.; Ishida, N.; Inamori, Y. Cytotoxicity of the hinokitiol-related compounds, gamma-thujaplicin and beta-dolabrin. *Biol. Pharm. Bull.* **2001**, *24*, 299–302.
22. Cavazza, M.; Pietra, F. A general entry to 10-halocolchicides and 9-halocolchicides. *Synth. Commun.* **1997**, *27*, 3405–3413.
23. Nozoe, T.; Someya, T. Reactive troponoid and o-aminophenol. II: The formation of cyclohepta[b][1,4]benzoxazine and 11H-cyclohepta[b][1,4] benzoxazin-10-one derivatives from isomeric isopropyl-2-chlorotropone. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3316–3319.