We anticipate the further study of related anilides and benzamides with the intent of testing further the generality of the correlations of chirality with amide CT and aromatic ^1L_a bands. Of particular interest are amides derived from the cis isomers of A and B and isomers of the phenylalanine analogue 1-amino-2-phenylcyclohexanecarboxylic acid.

Registry No.–H_2NCH_2Ph, 100-46-9; $H_2N(CH_2)_2Ph$, 64-04-6; $ClCOCH_2Ph$, 103-80-0; H_2NPh, 62-53-3; $H_2NC_6H_4$-p-CH_3, 106-49-0; $H_2NC_6H_4$-p-OCH_3, 104-94-9; $H_2NC_6H_4$-p-Cl, 106-47-8; $H_2NC_6H_4$-p-NO_2, 100-01-6; ClCOPh, 98-88-4; $ClCOC_6H_4$-p-CH_3, 874-60-2; $ClCOC_6H_4$-p-OCH_3, 100-07-2; $ClCOC_6H_4$-p-Cl, 122-01-0; $ClCOC_6H_4$-p-NO_2, 122-04-3; 2-phenylcyclohexane-1-carbonyl chloride, 34713-97-8; 1-amino-2-phenylcyclohexene, 37982-23-3.

References and Notes

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A General Synthesis of Terminal and Internal Arylalkynes by the Palladium-Catalyzed Reaction of Alkynylzinc Reagents with Aryl Halides

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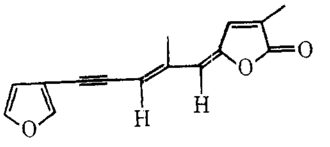
Arylalkynes represent a number of natural products such as freelingyne[1] (1) and junipal[2] (2). They have been most commonly prepared by Cu-promoted aryl–alkynyl coupling,[3] which involves either the reaction of alkynylcoppers with aryl halides[3a] or that of arylcoppers with alkynyl halides.[3b] More recently, an alternate approach consisting of the Pd-catalyzed reaction of alkynes with aryl halides in the presence of suitable bases has been developed.[4] While these known procedures are satisfactory in many cases, none of them appears to provide a satisfactory direct procedure for the synthesis of terminal arylalkynes which does not require any protection–deprotection sequence.[5] The difficulty largely stems from the fact that, under the reaction conditions, the required ethynyl reagents, such as ethynylcopper[6] and ethynylalkali metals,[7] are unstable with respect to disproportionation.



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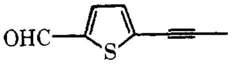

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We have recently found that organozinc compounds react rapidly with various aryl and alkenyl halides to produce cross-coupled products even at room temperature in the presence of a catalytic amount of a Pd or Ni catalyst, whereas the corresponding reactions of organoalkali metals and Grignard reagents are not only slower but generally less satisfactory.[8] We have also noted that ethynylzinc chloride can be conveniently prepared by the reaction of either ethynyllithium[7] or its ethylenediamine complex[9] with anhydrous zinc chloride as a reagent stable at room temperature.[10]

We now report that these findings can be exploited in developing a procedure for aryl–alkynyl coupling applicable even to the direct and selective synthesis of terminal arylalkynes (eq 1).

$$\mathrm{RC{\equiv}CZnCl + ArX \xrightarrow{\text{cat Pd complex}} RC{\equiv}CAr} \qquad (1)$$

$$\mathrm{R = H, alkyl, or\ aryl;\ X = I\ or\ Br}$$

The aryl–alkynyl coupling reaction reported here is essentially complete within several hours at room temperature when either aryl iodides or activated aryl bromides such as p-cyanobromobenzene are used. In such cases, the formation of arylalkynes proceeds cleanly without producing any other byproducts in significant amounts (<5%). On the other hand, unactivated aryl bromides such as bromobenzene are quite inert at room temperature. Thus, while the formation of tolan from 2-phenylethynylzinc chloride and iodobenzene is complete within 0.5 h at room temperature, the corresponding reaction of bromobenzene does not give any more than a trace of tolan even after 4 days under comparable conditions. Similar difficulties have also been observed with p-methoxybromobenzene and p-chlorobromobenzene. No aryl fluorides have been tested.

The present study corroborates our earlier finding that organozinc reagents are superior to the corresponding Grignard and organoalkali metal reagents in Pd or Ni-catalyzed cross-coupling.[8] Thus, for example, the reaction of 1-heptynylmagnesium bromide with o-iodotoluene gives only a 49% yield of 1-(o-tolyl)-1-heptyne after 24 h, and the corresponding reaction of 1-heptynyllithium does not produce the desired product in any more than a trace amount under comparable conditions. For the preparation of terminal alkynes, both ethynyllithium generated at −78 °C and its ethylenediamine complex serve as satisfactory sources of ethynylzinc chloride, although the latter appears to give somewhat cleaner results. In some experiments, 5 mol % of a Pd catalyst has been used. However, the subsequent studies have indicated that even 1 mol % of the catalyst gives entirely satisfactory results. Both $Pd(PPh_3)_4$ and a Pd catalyst generated in situ from $Cl_2Pd(PPh_3)_2$ and diisobutylaluminum hydride seem almost equally satisfactory. The use of $Pd(PPh_3)_4$, which does not require any additional treatment, is operationally simpler than that of the latter catalyst. On the other hand, the shelf-life of the former appears considerably shorter than that of the latter, although we have not yet determined how long $Pd(PPh_3)_4$ can be kept without a significant loss of its catalytic activity. Nickel–phosphine complexes, such as $Ni(PPh_3)_4$, do induce the desired cross-coupling reaction. However, the product yields have been low (<50%), and no complete consumption of aryl halides has been observed when the amount of the Ni catalyst is 5 mol %.[11] Unlike certain alkynylcoppers and related organotransition metals, which tend to be explosive, the Pd-catalyzed reaction of alkynylzinc derivatives does

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Table I. Preparation of Arylalkynes by the Pd-Catalyzed Reaction of Alkynylzinc Reagents with Aryl Halides[a]

$RC\equiv CZnCl$ R	Registry no.	Aryl halide (ArX) Ar	X	Registry no.	Catalyst,[b] (mol %)	Time, h	Yield of $ArC\equiv CR$,[c] % GLC	Isolated	Registry no.
H[d]	37008-61-0	*o*-Tolyl	I	615-37-2	A (5)	3	71		766-47-2
H[e]		*p*-Anisyl	I	696-62-8	A (5)	1	66	56	768-60-5
		Phenyl	I	591-50-4	A (1)	1	67		536-74-3
Methyl	64146-56-1	2-Thienyl	I	3437-95-4	A (1)	1	92	82	23229-66-5
n-Pentyl	64146-57-2	2-Thienyl	I		B (1)	2	85	70[f]	64146-58-3
		2-Thienyl	Br	1003-09-4	A (5)	48	75		
		p-Cyanophenyl	Br	623-00-7	A (1)	4	93		64146-59-4
		p-Cyanophenyl	Br		B (1)	4	82	[g]	
		p-Nitrophenyl	I	636-98-6	B (1)	3	94	64[h]	64146-60-7
		p-Anisyl	I		A (1)	0.5	92	70[i]	64146-61-8
		m-Tolyl	I	625-95-6	B (5)	1	89	79[j]	64146-62-9
		o-Tolyl	I		B (5)	1	88		64146-63-0
Phenyl	13984-49-1	*m*-Tolyl	I		B (5)	1.5	87	80[k]	14635-91-7
		Phenyl	I		A (1)	0.5	93	74[l]	501-65-5

[a] All reactions were run at room temperature in THF. The ratio of $RC\equiv CZnCl/ArX$ is 2 for the cases where R = H and 1 for $R \neq H$. [b] A = $Pd(PPh_3)_4$ and B = $Cl_2Pd(PPh_3)_2 + i\text{-}Bu_2AlH$. [c] All isolated products were identified by ^1H NMR, IR, and mass spectrometry. [d] Prepared from ethynyllithium generated at −78 °C in THF. [e] Prepared from ethynyllithium–ethylenediamine. [f] bp 74–76 °C (0.3 mm); $n^{28}{}_D$ 1.5482. [g] Isolated by GLC; $n^{25}{}_D$ 1.5500. [h] bp 105–110 °C (0.3 mm); $n^{23}{}_D$ 1.6676. [i] bp 114–115 °C (1.1 mm) [lit.[17] bp 92–93 °C (0.1 mm)]; $n^{25}{}_D$ 1.5409. [j] Isolated and purified by column chromatography; $n^{22}{}_D$ 1.5286. [k] mp 29–30 °C [lit.[18] mp 30–31 °C]. [l] mp 63 °C [lit.[19] mp 63.5 °C].

not appear to be associated with explosiveness, although this point is yet to be clearly established.

The synthetic usefulness of the new aryl–alkynyl coupling procedure may be demonstrated by the preparation in 81% yield (92% by GLC) of 1-(2′-thienyl)-1-propyne, which has previously been converted to junipal (**2**) via formylation.[12]

Experimental Section

All experiments were carried out under nitrogen atmosphere. All aryl halides and alkynes except acetylene were commercial reagents and used without further purification. Acetylene was purified by passing it through a dry ice–acetone trap, concentrated sulfuric acid, and potassium hydroxide pellets. THF was distilled over lithium aluminum hydride and stored over molecular sieves. Zinc chloride (Fisher Scientific Co.) was dried in an oven at 110 °C overnight before use. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer, and ^1H NMR spectra were recorded on a Varian T-60A spectrometer. GLC analyses were performed on a Hewlett-Packard 5750 gas chromatograph using a 6 ft × 0.125 in 5% SE-30 column on Chromosorb W. The GLC yields were determined using suitable hydrocarbon internal standards such as *n*-decane.

Palladium(0)–Phosphine Complexes. One of the palladium(0)–phosphine complexes was prepared from dichlorobis(triphenylphosphine)palladium(II) and diisobutylaluminum hydride.[8] The palladium(II) salt was in turn prepared from palladium chloride (25 mmol) and triphenylphosphine (60 mmol) by dissolving both of the compounds in DMF (160 mL) at 140 to 150 °C. On cooling, dichlorobis(triphenylphosphine)palladium(II) crystallized out of the solution. After filtration, the crystals were rinsed with ether and dried at reduced pressure.

Tetrakis(triphenylphosphine)palladium(0) was prepared according to the procedure reported by Coulson.[13]

Preparation of 1-Heptynylzinc Chloride. To a solution of 1-heptyne (20 mmol) in THF (10 mL) at 0 °C was added 20 mmol of *n*-butyllithium in hexane. The solution was stirred for 5 min followed by the addition of anhydrous zinc chloride (20 mmol) dissolved in THF (20 mL). The mixture was stirred for an additional 15 min at room temperature.

Preparation of Ethynylzinc Chloride from Ethynyllithium. THF (50 mL) was saturated with acetylene at −78 °C. *n*-Butyllithium (50 mmol) in hexane was diluted with THF (50 mL) and added dropwise to the acetylene solution at −78 °C. Maintaining the temperature at −78 °C, a solution of anhydrous zinc chloride (50 mmol) in THF (50 mL) was also added dropwise. The resulting mixture was then slowly warmed to room temperature.

Preparation of Ethynylzinc Chloride from Ethynyllithium–Ethylenediamine Complex. A suspension of 3.68 g (40 mmol) of ethynyllithium–ethylenediamine complex[9] in 40 mL of THF at 0 °C was charged with 5.46 g (40 mmol) of anhydrous zinc chloride dissolved in 40 mL of THF. The resulting slurry was warmed to room temperature and stirred for an additional 30 min.

Preparation of *p*-Methoxyphenylethyne. Ethynylzinc chloride was prepared as described above. To this were added sequentially at 0 °C 4.68 g (20 mmol) of *p*-iodoanisole dissolved in 20 mL of THF and 1.15 g (1.0 mmol) of $Pd(PPh_3)_4$ in THF (20 mL). The reaction mixture was stirred for 1 h at room temperature. GLC examination of an aliquot of the reaction mixture after quenching indicated the formation of the title compound essentially as the only volatile product. The remainder of the reaction mixture was quenched with 50 mL of 2 N HCl. After adding 50 mL of petroleum ether, the two layers were separated and the aqueous layer was extracted with petroleum ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered through a short alumina column to remove any trace of Pd-containing compound, and distilled under vacuum to give 1.48 g (56%) of *p*-methoxyphenylethyne (99% pure by GLC): bp 39–41 °C (0.7 mm) [lit.[14] bp 90–95 °C (10 mm)]; ^1H NMR (CCl_4, Me_4Si) δ 2.85 (s, 1 H), 3.72 (s, 3 H), 6.78 (d, $J = 8$ Hz, 2 H), 7.37 (d, $J = 8$ Hz, 2 H); IR (neat) 3250 (s), 2100 (m), 1600 (s), 1580 (s), 1450 (m), 1200 (s), 1240 (s), 1165 (s), 1025 (s), 830 (s) cm^{-1}.

Preparation of 1-(2′-Thienyl)-1-propyne. 1-Propynylzinc chloride was prepared by treating 1.10 g (24 mmol) of 1-propynyllithium[15] with 3.27 g (24 mmol) of anhydrous zinc chloride as described above. To a 250-mL flask equipped with a septum inlet, a magnetic stirring bar, and an outlet connected to a mercury bubbler were introduced 0.23 g (0.2 mmol) of $Pd(PPh_3)_4$ and 20 mL of THF. To this were added sequentially at 0 °C 5.04 g (3.06 mL, 24 mmol) of 2-iodothiophene and the above-prepared 1-propynylzinc chloride suspended in THF. The reaction mixture was stirred for 3 h at room temperature. GLC examination of a 1-mmol aliquot, after quenching with 5 mL of 2 N HCl, indicated the formation of the title substance in 92% yield. Neither the starting aryl iodide nor any other byproduct was observed in any more than a trace amount. The remainder of the reaction mixture (23 mmol) was quenched with 50 mL of 2 N HCl. After adding 50 mL of ethyl ether, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$, dried over $MgSO_4$, and distilled to give 2.30 g (82%) of 1-(2′-thienyl)-1-propyne (>99% pure by GLC): bp 73–75 °C (8 mm), $n^{23}{}_D$ 1.5919 [lit.[16] bp 65–66 °C (7 mm), $n^{17}{}_D$ 1.5950]; ^1H NMR ($CDCl_3$, Me_4Si) δ 1.99 (s, 3 H) 6.7–7.2 (m, 3 H); IR (neat) 2230 (w), 1430 (s), 1245 (s), 1195 (s), 1045 (s), 845 (s), 830 (s), 700 (s) cm^{-1}.

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Registry No.—1-Heptyne, 628-71-7; zinc chloride, 7646-85-7;

acetylene, 74-86-2; ethynyllithium–ethylenediamine complex, 50475-76-8; 1-propynyllithium, 4529-04-8.

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Heats of Hydrogenation of the Cis and Trans Isomers of Cyclooctene[1]

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Strain in organic molecules has long been of interest, and there are diverse ways of measuring its effect upon physical and chemical properties. With the advent of the powerful force field method for determining molecular structures and energies,[3] strained molecules have become a testing ground for those interested in this area of chemistry. The largest and most complete body of data available on the energies of molecules is to be found in the heats of formation of hydrocarbons.[4] These are ordinarily determined by measurement of heats of combustion. Since heats of combustion are large numbers and are measured relative to the elements, for which the heats of combustion are also large numbers, the experimental determination of the heat of formation of a compound involves a relatively small difference between two large numbers, and the experimental measurements must be of very high accuracy in order to secure heat of formation data which are of only moderate accuracy. This problem has long been recognized, and one solution is to measure the energy difference between two species in which one is interested, which is usually a much smaller quantity. In the case of unsaturated hydrocarbons, this is in principle easy. Heats of hydrogenation can be measured for alkenes and related compounds, and the heats of formation of the corresponding alkanes are usually known. Hence, the heat of hydrogenation can be determined directly to rather high accuracy, and the heat of formation can usually be obtained for the alkene with an accuracy approaching that which is available for the alkane. In practice there are some problems with experimental heats of hydrogenation. These can be determined in the gas phase, and this was the method used by Kistiakowsky in his classical investigations.[5] For experimental convenience, subsequent measurements have usually been made in acetic acid solution. This presents some interpretive difficulty. The experimental technique used by Turner[6] in his extensive studies on the heats of hydrogenation of alkenes is such that in order to convert his data to gas-phase numbers, one needs to know the heats of solvation of the alkanes obtained in acetic acid solution. These numbers are positive and often quite sizable since solvation of the hydrocarbon disrupts the liquid structure of the acetic acid. The heats of solvation are not usually known.

Recently, a technique for measuring heats of hydrogenation of unsaturated hydrocarbons in hexane solution at room temperature was developed.[7,8] The experimental technique is such that the directly measured number differs from the gas phase value only to the extent that the thermodynamic states of the reactant and product in very dilute hexane solution differ from the thermodynamic states of the gaseous product and reactant. We argue that the absence of differential intermolecular interactive forces makes this difference negligibly small. Hence, the values obtained pertain (to a very good approximation) to the actual molecular quantity desired, uncomplicated by solvation effects.

The cyclooctenes are a case of special interest in several ways. First, the heat of hydrogenation of *cis*-cyclooctene itself is known in the gas phase[5] and in acetic acid solution,[6] and these values can be compared with the value in hexane. More importantly, the trans isomer is a highly strained molecule, in which there is a bending (or rehybridization) deformation about the double bond.[9–11] Molecules with this deformation are scarce, hence the heat of hydrogenation of this compound is of interest. Since the heat of formation of cyclooctane is accurately known,[4] the heats of hydrogenation give us the heats of formation for these compounds.

Finally, there has been some question as to the structure of *trans*-cyclooctene.[9–12] The initial independently proposed structures arrived at from electron diffraction[11] and by molecular mechanics calculations[10] differed with respect to the stable conformation. More recent electron diffraction results[12] have borne out the calculations rather than the original electron diffraction results. We feel it is especially important that the energy of this molecule, as well as its structure, be accurately calculated by any force field which is going to be useful for strained alkenes.

We recently reported[13] a new force field (MM2) which utilized low-order torsional terms as a key feature and which was shown to work extremely well for calculation of the structures and energies of saturated hydrocarbons.[13,14] In extending this force field to alkenes, we noticed that we were not able to reproduce very well the heat of formation of *trans*-cyclooctene, as estimated from the heat of hydrogenation in acetic acid by Turner.[6] Our calculated structure was 2–3 kcal/mol more strained than Turner's heat of hydrogenation indicated.

It was concluded that it would be worthwhile to remeasure the heats of hydrogenation of the cyclooctenes in a hexane solvent so as to avoid the solvation problem. In addition, we now have available better criteria for determining the purity of the compounds than were available to Turner, and finally, we are now aware of the fact that *trans*-cyclooctene polymerizes to some extent upon distillation, and presumably also upon simply standing at room temperature. The purity of the samples was established by gas chromatography.

The heats of hydrogenation were determined, and the data are summarized in Table I. Indeed, the *cis*-cyclooctene value

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