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A Convenient Route to Unsymmetrical Conjugated Diynes

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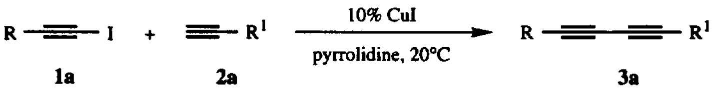
Abstract: Various unsymmetrical conjugated diynes can be prepared in good to excellent isolated yields by copper catalyzed coupling reaction of terminal alkynes with 1-iodo alkynes in pyrrolidine. In the case of 1-bromo alkynes, the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ improved the yield of coupling products. Copyright © 1996 Elsevier Science Ltd

The Cadiot-Chodkiewicz coupling of 1-bromo alkynes with terminal alkynes in the presence of copper (I) salt and an aliphatic amine has been reported to be a useful route to unsymmetrical 1,3-diynes.[1,2] However, this coupling is less successful when the reaction was carried out from 1-iodo alkynes[1a] or less acidic terminal alkynes (e.g., aliphatic 1-alkynes) and gives as side products symmetrical conjugated diynes, which are difficult to separate from the cross coupling products. Under palladium catalysis, the reaction of 1-halo alkynes with metal acetylides led to the formation of mixtures of homo and cross coupling products.[3,4] More recently, it has been reported that unsymmetrical 1,3-diynes may be prepared by coupling of 1-halo alkynes with terminal acetylenes by using a palladium water soluble catalyst[5] or a catalytic amount of $PdCl_2(PPh_3)_4$ and CuI.[6] We now report an efficient and convenient procedure for the preparation of unsymmetrical 1,3-diynes by copper catalyzed coupling of 1-halo alkynes with 1-alkynes in pyrrolidine. The reaction takes place rapidly and cleanly, at room temperature, without addition of palladium catalyst.

$$R{-}{\equiv}{-}X \quad + \quad {\equiv}{-}R^1 \xrightarrow[\text{pyrrolidine, 20°C}]{\text{10\% CuI}} R{-}{\equiv}{-}{\equiv}{-}R^1$$

R = C_5H_{11}, C_6H_5, $C_5H_{11}CH(OH)$
R^1 = CH_2OH, $(CH_2)_2OH$, $(CH_2)_4OH$, $(CH_2)_3Cl$, $(CH_2)_2COOMe$, C_6H_5, C_5H_{11}, CH_2NMe_2
X = I, Br

It is noteworthy that the nature of the amine is critical for the efficiency of coupling (table I). Thus, when 1-iodo-hept-1-yne **1a** (1 eq.) was treated at room temperature with 3-butyn-1-ol **2a** (2 eq.) and CuI (10%) in Et_3N, Et_2NH or $BuNH_2$, low yields of the diynes **3a** were obtained (20 to 54%, entries 1, 2 and 3). The coupling was also unsuccessful when using i-Pr_2NH or i-Pr_2NH-THF even under palladium catalysis[6] (25 to 30%, entries 4 and 5). However, switching to pyrrolidine,[7] the conjugated diyne **3a** was rapidly obtained in nearly quantitative isolated yield within 15 min. (95%, entry 7). Under the same conditions, piperidine gave 79% isolated yield of the diyne **3a** (entry 6). It may be pointed out that the use of Cadiot-Chodkiewicz conditions (5% CuCl, 30% NH_2OH, $EtNH_2$, $MeOH$-H_2O) led to a lower yield of unsymmetrical coupling product **3a** (77% instead of 95%, entries 7 and 8).



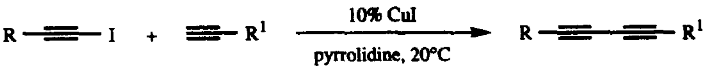
$R = C_5H_{11}$
$R^1 = (CH_2)_2OH$

Table I

Entry	Amine	Time	Isolated yield of **3a** (%)
1	Et_3N	24 h	20
2	Et_2NH	7 h	35
3	$BuNH_2$	6 h	54
4	i-Pr_2NH	3 h	25
5	i-Pr_2NH-THF	2 h	30[a]
6	piperidine	2 h	79
7	pyrrolidine	15 min	95
8	$EtNH_2$	15 min	77[b]

[a/] Reaction was carried out under Wityak conditions:[6] 3% CuI, 3% $PdCl_2(PPh_3)_2$, 2 equiv. i-Pr_2NH, THF. [b/] Reaction was carried out under Cadiot-Chodkiewicz conditions:[8] CuCl (5%), NH_2OH (30%), $EtNH_2$, $MeOH/H_2O$.

In order to show the efficiency of the procedure, a variety of unsymmetrical 1,3-diynes **3** were thus synthesized in good to excellent yields (61-98%, table II). As can be seen from table II, this useful reaction can be advantageously used in the case of aliphatic 1-alkynes (entries 15 and 19), and acetylenic alcohols $HC{\equiv}C(CH_2)_nOH$ with $n \geq 2$ (entries 7 table I and 13, 17 table II) which are known to give low yields of cross coupling products.[8]



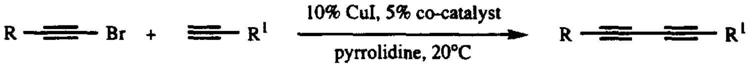
1 2 3

Table II

Entry	R	R^1	Isolated yield of 3 (%)
9	C_5H_{11}	C_6H_5	95
10	"	$(CH_2)_2COOMe$	98[a]
11	"	$(CH_2)_3Cl$	61
12	"	CH_2OH	95
13	"	$(CH_2)_4OH$	64
14	"	CH_2NMe_2	84
15	"	C_8H_{17}	70
16	"	CH(OH)Me	95
17	C_6H_5	$(CH_2)_2OH$	95[b]
18	"	CH_2OH	83[b]
19	$CH(OH)C_5H_{11}$	C_5H_{11}	70

a/ Yield of the corresponding amide. b/ Reaction was carried out at 0°C.

In a similar way, the coupling of 1-bromo alkynes **4** with 1-alkynes can also be performed in pyrrolidine (table III). It is noteworthy that under these conditions the use of $PdCl_2(PPh_3)_2$ (5%) as co-catalyst improved the yield of the reaction (91% instead of 74%, table III, entries 20 and 21).



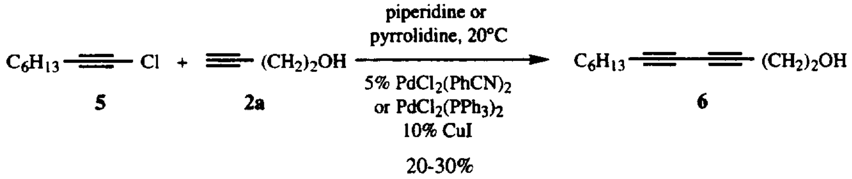
4 2 3

Table III

Entry	R	R^1	co-catalyst	isolated yield of 3 (%)
20	C_5H_{11}	$(CH_2)_2OH$	-	74
21	"	"	$PdCl_2(PPh_3)_2$	91[a]
22	"	CH_2OH	"	80
23	"	CH_2NMe_2	"	82
24	"	C_8H_{17}	"	61
25	"	C_6H_5	"	66

a/ by using Wityak[6] or Cadiot-Chodkiewicz[8] conditions, the diyne **3a** was obtained respectively in 40 and 75% isolated yield.

Under the same conditions, 1-chloro alkyne **5** showed a lower reactivity toward alkyne **2a** and gave low yield of unsymmetrical 1-3-diyne **6** (30%) even by using $PdCl_2(PhCN)_2$-CuI in piperidine which is an efficient catalytic system in the case of coupling reaction of vinyl chlorides with 1-alkynes.[9]



In conclusion, the procedure described here provides an efficient and simple route, under mild conditions, to unsymmetrical 1,3-diynes. Furthermore, the results obtained may be favourably compared with those obtained by existing methodologies.

Typical procedure for the preparation of undeca-3,5-diyn-1-ol (3a): To a stirred solution of (E)-1-iodo-1-hept-1-yne **1a** (222 mg, 1 mmol) and but-3-yn-1-ol **2a** (140 mg, 2 mmol) in pyrrolidine (1.5 ml), under an argon atmosphere, was added copper iodide (19 mg, 0.1 mmol). After stirring at room temperature for 30 min, the mixture was hydrolysed with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic extract was dried over $MgSO_4$ and the solvent was removed *in vacuo*. Filtration through silica gel (elution petroleum ether : ethyl acetate, 6:4) gave 155 mg (95%) of pure 1,3-diyne **3a**[10] (table I, entry 7).

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