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Alkylation of 1-alkynes in THF

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Abstract—Alkynes may be easily alkylated by sequential treatment with *n*-BuLi followed by an alkyl halide in THF. Primary iodides give excellent yields (75–99%) as do bromides in the presence of catalytic amounts of Bu_4NI or NaI; in the absence of an iodide source, bromides react poorly. This method offers advantages over existing methods which use HMPA or NH_3 as co-solvents.

A classic method for the formation of carbon–carbon bonds is the alkylation of metal acetylides with alkyl halides.[1] Traditionally, this reaction was carried out in liquid NH_3[2] but problems with acetylide solubility and variable yields led to the development of alternative reaction conditions. Particularly noteworthy was the introduction of hexamethylphosphoramide (HMPA) as a dipolar aprotic solvent for promoting such S_N2 reactions in 1973.[3] Since that time, HMPA has been shown to be a potential health hazard as a carcinogen. Thus, *N*,*N*′-dimethylpropyleneurea (DMPU) was examined as a safer and comparably efficacious alternative in 1988.[4] Such alkylations have also been carried out in dimethylsulfoxide (DMSO) but, unfortunately, the acidity of DMSO limits the reaction to relatively acidic alkynes (e.g. PhC≡CH, $THPOCH_2C{\equiv}CH$).[5] Based on safety and/or convenience concerns, one might expect that HMPA and NH_3 would not be particularly popular solvent choices, but a survey of the recent literature revealed that the vast majority of alkyne alkylations are carried out using HMPA as a co-solvent[6] with NH_3 also used regularly[7] and DMPU[8] used only rarely. We now report that, under the appropriate conditions, the ubiquitous solvent THF may be used and virtually any 1-alkyne may be alkylated with excellent results.

In examining the conditions reported for the alkylation of alkynyllithiums, it became apparent that the use of a dipolar aprotic solvent or NH_3 is not necessary if the alkyl halide is particularly reactive (e.g. MeI,[9] allylic,[10] or $ROCH_2X$[11]). Similarly, alkynyllithiums add to carbonyl compounds readily in THF (at low temperatures).[12] Thus, it was clear from the results presented in the literature that the range of conditions employed for alkynylations is related principally to reactivity: with very reactive carbonyl compounds, reactions occur in THF at −78°C; with reactive halides, reactions take place in THF at rt or below. An obvious extension (which seems not to have been explored) is then to use THF at elevated temperatures with 'regular' alkyl halides rather than introducing a more polar solvent to promote the S_N2 reaction. Part of the reluctance to use THF as a solvent with 'regular' alkyl halides is likely due to the observation that alkynyllithiums 'react sluggishly in Et_2O or THF with most alkyl halides'.[13] Moreover, it has been reported that refluxing dioxane (which is similar to THF) is a mediocre medium for these reactions, especially with volatile alkyl halides.[4,14] However, with the limitations of the other methods currently used and the ready availability of dry THF, we felt that it was worthwhile to re-examine this solvent for alkynylations.

Initial studies were carried out using 1-hexyne, which was readily converted (*n*-BuLi) to the lithium acetylide. As expected, alkylations of 1-hexynyllithium (Table 1, entries 1–7) were very slow at ambient temperatures. However, simply warming the reaction mixture to reflux temperatures allowed for complete reaction within 8 h for primary iodides (entries 1 and 4). Bromides were much slower and gave incomplete reactions, even after extended periods (entry 2). However, it was gratifying to discover that the addition of a catalytic amount of *n*-Bu_4NI (TBAI) or NaI to these reactions had a dramatic effect: reactions now proceeded to completion with reaction times only slightly longer than when iodides are used (entries 3 and 6). The use of an iodide source (presumably to form small amounts of more reactive alkyl iodides via Finkelstein reactions) to

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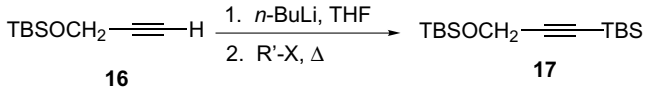
promote S_N2 reactions is well-known, particularly in ether synthesis.[15] However, with a primary chloride (entry 5), even TBAI did not enhance reactivity sufficiently to provide a good yield of alkylation product.

A number of other alkynes were alkylated with bromides and iodides in THF at reflux temperatures (Table 1). In all cases, reactions were very clean with no detectable (GC–MS and TLC) side products and excellent isolated yields were obtained. Both TBAI and NaI were equally effective in promoting alkylations with bromides (entries 12 and 13), an unexpected result given the limited solubility of NaI in THF. With TBAI, traces of Bu_3N were sometimes detected in crude reaction mixtures (by GC–MS) but did not interfere with product isolation (since it would be lost during the aqueous work-up). It is noteworthy that THP ethers, protecting groups very commonly used in syntheses of long chain unsaturated pheromones, are tolerated in both the alkyne and alkyl halide (entry 7, 14–21). A THP-protected propargyl alcohol (entries 14 and 15) showed lower reaction rates, likely due to stabilization of the alkynyllithium by the neighbouring THPO.[5] Other THP-protected alkynyl alcohols showed reactivities comparable to hydrocarbon 1-alkynes.

Successful alkylations using ethyl iodide (bp 69–73°C, entries 17 and 19) are significant (but not too surprising since THF boils at 66°C) given the poor results noted previously when elevated temperatures (boiling dioxane, 100°C) were used with low boiling alkyl halides.[4] The successful use of ethyl bromide (bp 40°C) was unexpected but suggests that alkylations of alkynes in THF are not limited to high-boiling alkyl halides. In fact, given that MeI reacts at or below room temperature, one should be able to introduce essentially any length of alkyl group using this procedure.

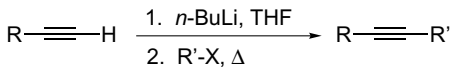
There are some limitations to this chemistry. For example, it seems to be limited to primary halides: no reaction was observed when 1-hexynyllithium was treated with 2-iodooctane in refluxing THF for 24 h. With a homoallylic halide (Table 1, entry 22), considerable amounts of starting alkyne were isolated, likely due to a competing E_2 pathway. Nonetheless, the desired alkylation product **15** was produced in reasonable yield; this compares very favourably to a comparable reaction using the same halide in HMPA that afforded a 19% yield of product as a mixture of isomers.[3] The only other limitation observed was when the silyl-protected propargyl alcohol **16** was used (Eq. (1)): a mixture of products was formed including alkynylsilane **17**,[16] suggesting that TBS groups are incompatible.



16 **17**

(1)

Table 1. Alkylation of 1-alkynes in THF[a]



Entry	R	R′-X	Additive[b]	Time (h)	Product	Yield (%)[c]
1	n-C_4H_9	n-$C_{10}H_{21}I$	–	8	**1**	75
2	n-C_4H_9	n-$C_{10}H_{21}Br$	–	18	**1**	50[d]
3	n-C_4H_9	n-$C_{10}H_{21}Br$	TBAI	12	**1**	95
4	n-C_4H_9	n-$C_5H_{11}I$	–	9	**2**	88
5	n-C_4H_9	n-$C_7H_{15}Cl$	TBAI	60	**3**	52
6	n-C_4H_9	n-$C_7H_{15}Br$	NaI	15	**3**	90
7	n-C_4H_9	$THPO(CH_2)_9Br$	NaI	16	**4**	85
8	t-C_4H_9	n-$C_{10}H_{21}I$	–	7	**5**	86
9	t-C_4H_9	n-$C_{10}H_{21}Br$	NaI	11	**5**	85
10	t-C_4H_9	n-$C_7H_{15}I$	–	7	**6**	84
11	Ph	n-$C_{10}H_{21}I$	–	12	**7**	99
12	Ph	n-$C_5H_{11}Br$	TBAI	16	**8**	90
13	Ph	n-$C_5H_{11}Br$	NaI	16	**8**	86
14	$THPOCH_2$	n-$C_{10}H_{21}I$	–	33	**9**	89
15	$THPOCH_2$	n-$C_{10}H_{21}Br$	NaI	40	**9**	83
16	$THPO(CH_2)_2$	n-$C_{10}H_{21}I$	–	11	**10**	94
17	$THPO(CH_2)_2$	EtI	–	2	**11**	91
18	$THPO(CH_2)_4$	n-$C_{10}H_{21}I$	–	11	**12**	89
19	$THPO(CH_2)_4$	EtI	–	2	**13**	93
20	$THPO(CH_2)_4$	EtBr	NaI	8	**13**	92
21	$THPO(CH_2)_4$	n-C_3H_7I	–	3	**14**	94
22	$THPO(CH_2)_4$	$CH_2{=}CHCH_2CH_2Br$	NaI	16	**15**	55

[a] See text for details.
[b] 10 mol% TBAI or NaI added.
[c] Isolated yields of purified products.
[d] GC yield.

Overall, while not universally applicable, this procedure is operationally very simple, uses common reagents and solvents, and is very effective. It should be adopted as the method of choice for many alkyne alkylations.

A typical experimental procedure follows: To a cold (−78°C), stirred solution of 1-alkyne (12 mmol) in THF (50 mL) was added *n*-BuLi (1.6 M in hexanes, 11 mmol).[17] The solution was allowed to warm to room temperature before adding alkyl halide (10 mmol along with 1 mmol of NaI or TBAI for bromides). The reaction mixture was heated to gentle reflux and stirred until all of the alkyl halide was consumed (GC or TLC, 8–40 h). The mixture was cooled to 0°C and quenched with satd NH_4Cl. Standard aqueous work-up (ether, satd NH_4Cl) provided crude material, which was >90% pure (GC) in most cases. Purification was effected by Kugelrohr distillation or flash chromatography.[18]

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