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Synthesis of Propargylic Ethers via *Lewis*-Acid Mediated Nucleophilic Substitution of Propargylic Esters

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Abstract: Direct displacement of propargylic esters is reported. 10 mol% of $TiCl_4$ were used to carry out this novel, nucleophilic substitution.
Keywords: alkynes; substitution; ethers; catalysis.

A range of metal-catalyzed reactions of propargylic compounds are known,[1] in particular palladium-catalyzed reactions.[2] Most of these reactions yield in the corresponding allenic systems and subsequent rearranged derivatives. But only little is known about the nucleophilic substitution of the propargylic system. Reactions of propargylic acetates with C-nucleophiles were described by Macdonald et al.[3] They used alkylcuprates in this process for C-C-bond formation. Displacement reactions by using cobalt complexes of propargylic alcohols were described by Nicholas et al.[4] Several nucleophiles were reacted with the $Co_2(CO)_8$ complexes to give the substituted propargylic compounds.
Herein we describe a simple, direct nucleophilic substitution of propargylic ester. During our investigations to the rearrangement of the propargylic system[5] we found that *Lewis* acids mediate the nucleophilic substitution of propargylic acetates. High yields were obtained by $TiCl_4$-mediated displacement reactions.

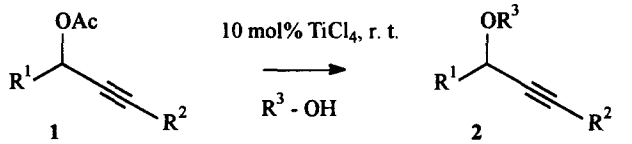

Table 1. Reactions of propargylic acetates with alcohols[6]

entry	R^1	R^2	R^3	product	yield / %
1	Ph	Ph	Me	**2a**	95[8]
2	Ph	Ph	Et	**2b**	65[9]
3	Ph	Ph	*i*Pr	**2c**	59
4	Ph	Ph	*t*Bu	**2d**	55
5	Ph	*n*Bu	Ph	**2e**	45
6	Ph	*n*Bu	Me	**2f**	76[10]
7	Ph	*n*Bu	Et	**2g**	68[11]
8	Ph	*n*Bu	*i*Pr	**2h**	42

In order to determine the scope and limitations of this reaction, other nucleophiles were also examined. A decrease in yield is observed with alcohols in the order of MeOH, EtOH, *i*PrOH, *t*BuOH. At the same time an increasing formation of hydrolysis products arises. Substances derived from the formation of the corresponding allenic system or from rearrangement could not be detected.[5,7] Even alcohols with a low degree of

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nucleophilicity resulted in the expected ether in good yields under these reaction conditions (Table 1, entry 5). In addition the successful performance of this reaction depends on the substituents R^1 and R^2 in the propargylic moiety. High yields were observed by reacting diphenylsubstituted propargylic esters (Table 1, entries 1 - 4) whereas lower yields were observed in reactions of monophenyl-substituted propargylic esters (Table 1, entries 5 - 8). No reactions were obtained in $TiCl_4$-mediated reactions, if R^1 represents an alkyl substituent. The decreasing stabilization of the formed cation during the reaction seems to be responsible for this tendency. Products derived from hydrolysis were mostly obtained.

One can overcome this problem by using catalytic amounts of trifluoromethansulfonates as *Lewis*-acids in these displacement reactions. By using 10 mol% of trimethylsilyltriflate, the propargylic methylether is obtained in about 40 % yield (R^1=*n*Pr, R^2=Ph, R^3=Me). Similiar results were obtained in reactions of equimolar amounts of the very unstable propargylic triflates with alcohols.[12]

Further investigations on the mechanism and the enantioselective execution of this new reaction are under way.

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6. All new compounds have been satisfactorily charaterized (^{1}H NMR, ^{13}C NMR, MS, elemental analysis). Preparation of 1-phenyl-1-*iso*propoxyhept-2-yne **2h**: $TiCl_4$ (42 mg, 0.22 mmol) was carefully added to a stirred solution of 1-phenyl-1-acetoxyhept-2-yne (0,5 g, 2.2 mmol) in abs. *iso*PrOH (5.0 mL). The reaction mixture was stirred for 24 h at r.t. and after completion (TLC control) extracted several times with diethyl ether and aqu. $NaHCO_3$ solution. The org. layers were separated, concentrated i. vac. and purified by chromatography. 200 mg (42 %) of the isopropyl ether were isolated as a colorless oil. ^{1}H NMR ($CDCl_3$/TMS) 0.78 (t, J= 7.2, 3H, CH_3-6), 1.07 (d, J= 6.0, 3H, 1x CH_3-*i*Pr), 1.11 (d, J= 6.4, 3H, 1x CH_3-*i*Pr), 1.22- 1.47 (m, 4H, 2x CH_2), 2.13 (t, J= 7.2, 2H, CH_2-4), 3.85 (q, J= 6.0, 1H, CH-*i*Pr), 5.07 (s, 1H, H-1), 7.14- 7.39 (m, 5H, C_6H_5). ^{13}C NMR ($CDCl_3$/TMS) 13.6 (CH_3-7), 18.6 (CH_2-4), 21.7 22.8 (2x CH_3-*i*Pr), 21.9 (CH_2), 30.7 (CH_2), 69.1 (C-0), 69.2 (CH-O), 78.9 (C-3), 87.4 (C-2), 127.3 127.9 128.3 (CH_{arom}), 140.3 (C_{arom}). MS: m/z (%) 231 (M^++1, 3), 230 (M^+, 13), 187 (14), 171 (20), 145 (22), 129 (51), 115 (38), 105 (100), 91 (58), 77 (61), 57 (50), 43 (51)

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