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CONJUGATE ADDITION OF ORGANOCOPPER REAGENTS TO N-TOSYLATED α, β-UNSATURATED AMIDES

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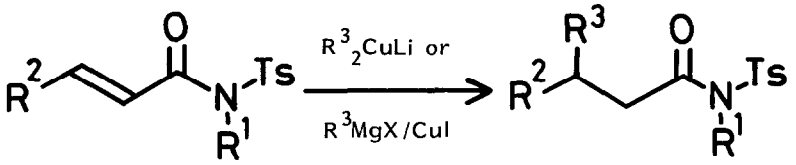
Summary: N-Tosylated α, β-unsaturated amides and lactams undergo facile conjugate addition with R^2CuLi or RMgX/CuI (cat.). Stereoselective synthesis of *trans*-β,γ-dialkyl-γ-lactams can be achieved by this procedure. The resulting N-tosylamide moiety is further transformed to alcohol and several carbonyl compounds by way of reduction or nucleophillic displacement.

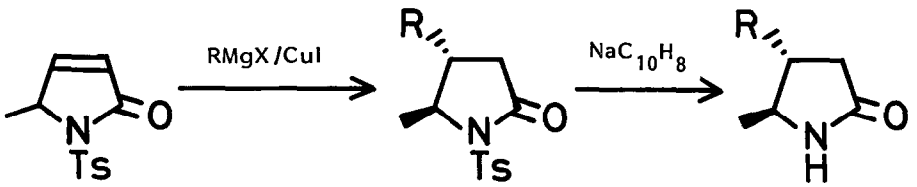
Although conjugate addition of organometallic reagents to unsaturated carbonyl compounds have been well elaborated as a synthetic tool for the carbon-carbon bond formation, a little has been known on that to unsaturated amide derivatives.[1] Recently, Baldwin,[2] Snieckus,[3] and Mukaiyama[4] reported successful 1,4-addition of organolithium compounds and Grignard reagents to several acyclic unsaturated amides; however, no comment was given on that to conjugated lactams. In the course of other investigation, we required β-substituted γ-lactams, and attempted conjugate addition of several organometallic reagents to N-alkyl-α,β-unsaturated γ-lactams. To our surprise , the deprotonation of γ-proton of the lactam predominantly took place, yielding the corresponding β,γ-unsaturated lactam after aqueous work-up. In this paper, we wish to report that N-tosylated α,β-unsaturated amides and lactams are versatile substrates for the conjugate addition with organocopper reagents. This process provides not only a solution to the introduction of a β-alkyl moiety to lactam but also a new synthetic method for β-substituted alcohols, aldehydes, ketones, and other carbonyl functions by way of subsequent transformations of the resulting amides.



Ts = p-$MeC_6H_4SO_2$-
R^1,R^2,R^3 = alkyl, aryl

In Table 1 are summarised typical examples of the conjugate addition. Methyl, butyl, or phenyl groups were introduced successfully with either R^2CuLi at -78 °C or a combination of RMgX and a catalytic amount of CuI at -20 °C. Use of organocopper reagents is crucial, and hard nucleophiles such as RLi and RMgX resulted in exclusive 1,2-addition to the carbonyl function. The reaction can be applied to unsaturated lactams, of which N-alkyl analogues did not give the conjugated adducts.

Of particular interest is that stereoselectivity of the addition to certain unsaturated lactams where a neighboring substituent is present. In fact, it is well-known that *trans*-selective addition takes place in the reaction of unsaturated lactones with organocopper reagents.[5] Treatment of N-tosyl-γ-methyl-α,β-unsaturated γ-lactam (9) with PhMgBr and CuI (5 mol%) afforded 10a as a single diastereo isomer. Deprotection of the tosyl group by $NaC_{10}H_8$[6] led to the known lactam 11a, in which the stereochemistry of two substituents is *trans*.[7] Similarly, reaction of 9 with p-$MeOC_6H_4MgBr$/CuI proceeded with high stereoselectivity to form *trans*-adduct 10b in 74% yield.[8]



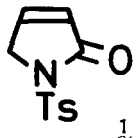
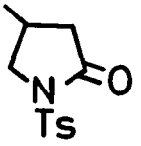
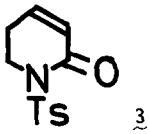
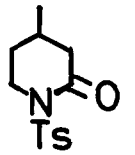
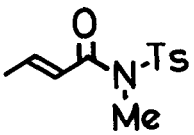
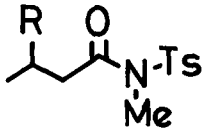
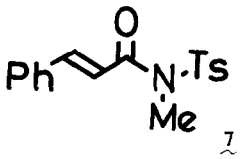
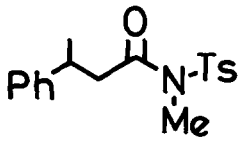
9

R = Ph (10a) 70% R = Ph (11a) 74%
R = p-$MeOC_6H_4$- (10b) 74% R = p-$MeOC_6H_4$- (11b) 63%

Usually the amide carbonyl is reluctant to the attack of nucleophiles because of electron donating character of nitrogen. Introduction of tosyl group on the nitrogen atom reduces the donating character, enhancing the electrophilicity of the carbonyl function. Thus, the resulting N-tosylated amides can be expected further transformation with nucleophiles.[9] The results exemplified by 8 are outlined in Scheme 1. Reduction of 8 with $NaBH_4$ in ethanol gave the corresponding alcohol in 73% yield. While treatment with 1 eq. of DIBAL in THF-toluene afforded the aldehyde in 77% yield. Nucleophilic displacement with OH, OMe, or amine was accomplished under basic conditions to give 14, 15, and 16 in 63, 99, and 93% yields, respectively. Reaction with excess RMgX afforded the corresponding tertiary alcohol, but controlled addition of 1 eq. of the reagent in THF gave the ketone in 60-80% yields. On the other hand, reductive detosylation was successfully accomplished with $NaC_{10}H_8$ in DME.

Above results show that N-tosylated α,β-unsaturated amides undergo facile conjugate (1,4-) addition with soft nucleophiles (organocopper reagents), and after work-up, the resulting amides undergo 1,2-addition with hard nucleophiles. This sequence of the reactions provides that N-tosylated α,β-unsaturated amides are regarded as a "$^+CH_2CH_2CO^+$" synthon.

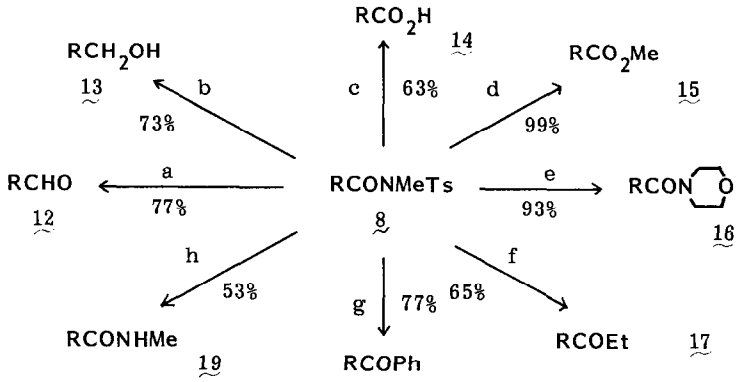
Table 1. [a]

Substrate	Nucleophile	Product	Yield (%)
 1	MeMgI/CuI	 2	73
 3	MeMgI/CuI	 4	70
 5	Me_2CuLi	 6	83 (R = Me)
	MeMgI/CuI		79 (R = Me)
	Bu_2CuLi		74 (R = n-Bu)
	PhMgBr/CuI		76 (R = Ph)
 7	MeMgI/CuI	 8	81
	Me_2CuLi		0 [b]

a) General procedure: To an etherial solution of RMgX (1.5 - 2N, 3 mmol) was added CuI (0.1 mmol, 19 mg) at -5 °C and the mixture was stirred for 10 - 15 min. Then the solution was cooled to -20 °C and amide (1.8 mmol) in ether (2 mL) was added. After stirring the solution at -20 °C for 2.5 h, excess RMgX was destroyed by aqueous NH_4Cl. The mixture was extracted by ether, and the organic layer combined was washed with brine, dried over $MgSO_4$, and concentrated. Chromatographic purification (silica-gel, hexane-ether) afforded the product. In the cases with R_2CuLi, cuprates were prepared according to the literature,[1] and the reaction was carried out at -78 °C. Reductive detosylation was carried out as follows; naphthalene (1.8 mmol, 233 mg) was dissolved in DME. Na (1.8 mmol, 42 mg) was added to the solution, and the mixture was stirred for 2 h. Dark green $NaC_{10}H_8$ was formed. Tosyl amide (0.3 mmol) dissolved in DME was added at 0 °C, and the mixture was warmed slowly to room temperature with stirring. After the reaction was complete (ca. 1 h), water was added, and the mixture was extracted with ether. The extracts combined were washed with brine, dried over $MgSO_4$, and concentrated. Chromatography on Al_2O_3 of the residue by CH_2Cl_2-hexane afforded the desired amides.

b) Reductive detosylation to form N-methylcinnamoylamide took place.

Scheme 1.



R = $PhCH(CH_3)CH_2$-

a. DIBAL/toluene-THF/-78 °C; b. $NaBH_4$/ethanol/r.t.; c. NaOH aq./MeOH/r.t.; d. NaOMe/anhydrous MeOH/r.t.; e. morpholine/THF/reflux; f. C_2H_5MgBr/THF/-78 °C; g. C_6H_5MgBr/THF/-78 °C; h. $C_{10}H_8Na$/DME/0 °C - r.t.

References and Notes

1) For a review, G. H. Posner, Organic React., 19, 1 (1972)

2) J. E. Baldwin and W. A. Dupont, Tetrahedron Lett., 21, 1881 (1980)

3) G. B. Mpango, K. K. Mahalanabis, Z. Mahdavi-Damghani, and V. Snieckus, Tetrahedron Lett., 21, 4823 (1980)

4) T. Mukaiyama and N. Iwasawa, Chem. Lett., 913 (1983)

5) J. P. Vigneron, R. Méric, and M.Dhaenens,Tetrahedron Lett., 21, 2057 (1980)

6) S. Ji, L. B. Gortler, A. Waring, A. Battisti, S. Bank , W. D. Closson, and P. Wriede, J. Am. Chem. Soc., 89, 5311 (1967)

7) H. Bruderer, W. Arnold, and W. E. Oberhansli, Helv. Chim. Acta, 61, 118 (1978)

8) The stereochemistry was determined by comparison of the spectral data of 11b with those of the known lactam.[7] Stereoselective addition was also observed in the reaction of 9 with MeMgI/CuI or BuMgI/CuI, giving the corresponding adducts as a single diastereoisomer. (70 - 90% yields) It seems reasonable that the stereochemistry of these adducts is *trans*.

9) It has been reported that introduction of certain electron-withdrawing group on amide nitrogen facilitates nucleophilic displacement. See, Y. Nagao, T. Ikeda, M. Yagi, E. Fujita, and M. Shiro, J. Am. Chem. Soc., 104, 2079 (1982) ; T. Izawa and T. Mukaiyama, Chem. Lett., 1443 (1977); D. L. Flynn, R. E. Zelle, and P. A. Grieco, J. Org. Chem., 48, 2424 (1983); D. A. Evans, J. Bartroli, and T. L. Shih, J. Am. Chem. Soc., 103, 2127 (1981)

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