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ALKYLATION OF α,β-UNSATURATED AMIDES VIA METALATED AND DIMETALATED INTERMEDIATES

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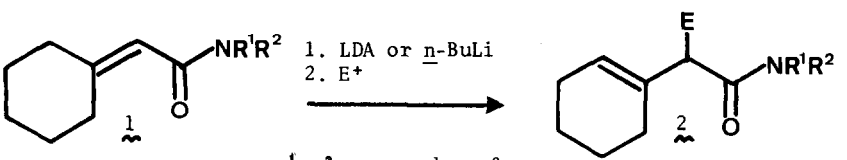
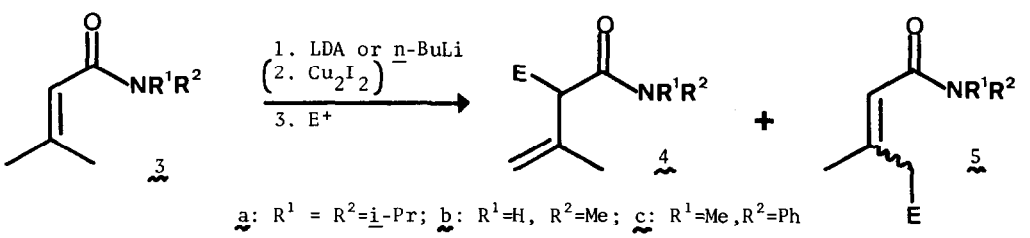
In spite of the early work of Hauser,[1] the potential utility of metalated carboxamides in organic synthesis has been only recently recognized.[2] During the course of synthetic efforts in the indole alkaloid area, we discovered and used to advantage a regioselective γ-alkylation reaction of a heterocyclic dimetalated α,β-unsaturated amide.[3] Consequently, we have examined the alkylation of unsaturated amides 1a,b and 3a,b via metalated and dimetalated intermediates. In this Letter we show that the unsaturated amide is a generally useful synthon in regio- and stereo-selective C-C bond forming operations.[4]

Selected alkylation experiments with the cyclohexenyl acetamide substrates 1a and 1b (Table 1) demonstrate that the derived mono- and di-lithiated species provide deconjugative α-substituted products 2a and 2b respectively using primary, secondary, allylic, and benzylic halides as well as benzaldehyde, methyl benzoate, and phenylselenyl bromide. Isopropyl iodide and 1,3-dichloro-2-butene failed to alkylate dilithiated 1b.

Whereas some of the reactions of 1a,b are sluggish, mono- and di-lithiated senecioamides 3a,b undergo rapid and efficient alkylation to give mainly α-products 4 (Table 2). In particular, diisopropyl amide 3a is alkylated within minutes at room temperature reflecting the



a: $R^1=R^2$=Me; b: R^1=H, R^2=o-MeC_6H_4



a: $R^1 = R^2$=i-Pr; b: R^1=H, R^2=Me; c: R^1=Me, R^2=Ph

TABLE 1

Substrate	E	Yield[a]
1a	Me	58%
1a	i-Pr	83%
1a	$Me_2C=CHCH_2$	71%
1a	$MeC(Cl)=CHCH_2$	73%
1a	PhCH(OH)	68%[b]
1a	PhCO	43%
1a	PhSe	32%
1b	Me	80%
1b	$Me_2C=CHCH_2$	71%
1b	$PhCH_2$	43%
1b	PhCH(OH)	45%[c]

[a] Isolated yields after purification by column chromatography (SiO_2) or distillation; < 3% γ-products were detected (glc). [b] Erythro: threo = 1:3 (nmr) formed under thermodynamic control (4 h) cf. ref. 5. [c] Erythro: threo = 8:1 formed under kinetic control (40 min), cf. ref. 5. Longer reaction times give the corresponding ketone and $PhCH_2OH$ presumably by a Cannizzaro reaction.

TABLE 2

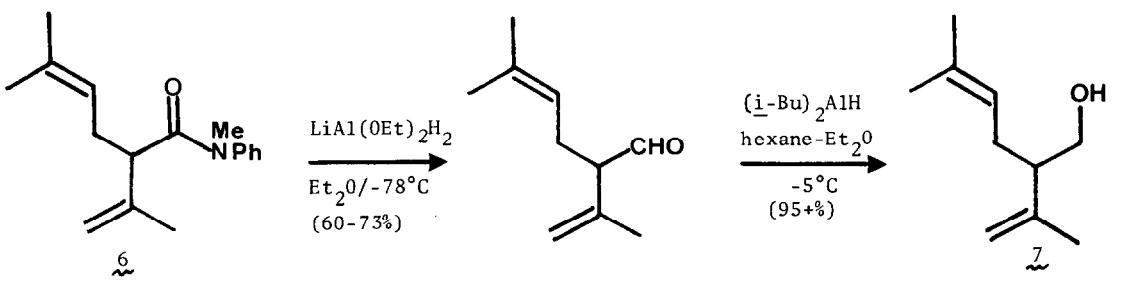
Entry	Substrate	Metal	E	Yield[a]	Regioselectivity[b] 4 / 5	γ-Stereoselectivity[b,c] 5Z / 5E
1	3a	Li	Me	98%	98 / 2	
		Cu		97%	98 / 2	
2	3a	Li	i-Pr	97%	86 /14	93 / 7
3	3a	Li	$Me_2C=CHCH_2$	93%	96 / 4	undetermined
		Cu		89%	41 /49[d]	85 /15[e]
4	3a	Li	$PhCH_2$	97%	98 / 2	
5	3b	Li	Me	98%	98 / 2	
		Cu		95%	53 /43[d]	91 / 9
6	3b	Li	i-Pr	95%	82 /16.5[d]	91 / 9
		Cu		97%	49 /48[d]	78 /22
7	3b	Li	$CH_2=CHCH_2$	91%	98 / 2	
		Cu		84%[f]	9 /78[d]	86 /14
8	3b	Li	$Me_2C=CHCH_2$	90%[g]	92 / 8	unresolved
		Cu		87%[f]	6 /90[d]	81[h]/19
9	3b	Li	$PhCH_2$	90%	98 / 2	
		Cu		97%	31 /60[d]	87 /13
10	3c	Li	$Me_2C=CHCH_2$	92%	98 / 2	

[a] Total isolated yield after chromatography (SiO_2) or distillation. [b] Determined by glc and nmr (including benzene-induced chemical shift studies). [c] Z,E isomer mixtures have not been separated on a preparative scale. [d] Contains minor amounts (glc) of another component which has not been characterized. [e] Transposed (S_N2') product, $2Z\text{-}CH_2=C(Me_2)CH_2C(Me)=CHCON(iPr)_2$, cf. ref. 6. [f] Constitutes yield of γ-product only. [g] Constitutes yield of α-product only. [h] Contains traces of transposed (S_N2') product, cf. ref. 6.

steric constraints imposed by the N-substituents which are released upon deconjugation. Reactions of i-PrI with lithiated 3a and 3b also yield more than trace amounts of γ-alkylated products (5) (Entries 2,6).

γ-Regioselectivity is significantly enhanced by using the cuprated species of 3a and 3b generated under conditions developed by Katzenellenbogen for γ-selective alkylation of unsaturated carboxylic acids.[6,7,8] Thus although cuprated 3a undergoes α-methylation irrespective of cation (Entry 1), a shift towards γ-regioselectivity is evident in the prenylation reaction (Entry 3). γ-Alkylation is even more pronounced with dicuprated 3b: MeI, i-PrI, and $PhCH_2Br$ give about equal amounts of α- and γ-substituted products (Entries 5,6,9), while predominantly γ-alkylation is observed with $CH_2=CHCH_2Br$ and $Me_2C=CHCH_2Br$ (Entries 7,8). In both series, 3a and 3b, the γ-products show high degree of Z-stereoselectivity (formation of thermodynamically less stable isomer). Comparison of our data with that of Katzenellenbogen[6a] shows that dicuprated unsaturated amides (3b) and acids are both highly γ-regioselective in reactions with allylic halides. However, 3b also exhibits γ-selectivity with non-allylic halides MeI, i-PrI, and $PhCH_2Br$. Furthermore, high Z-stereoselectivity is achieved in γ-alkylations of 3b using allylic halides in contrast to the results obtained with the corresponding senecioic acid.[6] Of mechanistic interest is the fact that monocuprated unsaturated esters undergo exclusively α-regioselective reactions with MeI, $PhCH_2Br$, and $Me_2C=CHCH_2Br$.[9] The corresponding monocuprated 3a tends towards γ-selectivity with only a minor component of transposed (S_N2') product (Entry 3). Further work may reveal a mechanistic divergence in unsaturated amide vs ester alkylation reactions.

The utility of α-alkylation products is demonstrated by the efficient two-stage reduction[10] of the prenylated product 6 (Entry 10) into the irregular monoterpenoid lavandulol (7).[11] Application of the highly γ-regio- and stereo-selective prenylation reaction (Entry 8) to the construction of terpenoid natural products is under investigation.



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We conclude that alkylation of α,β-unsaturated amides via metalated and dimetalated intermediates is a viable general method for C-C bond formation. Its scope is enhanced by the availability of amide into acid, ester, aldehyde, ketone, and amine conversions.[12] Finally, since the α-alkylation reaction can be carried out conveniently at 0°C or room temperature without suffering self-condensation and 1,2- or 1,4-addition, it has some advantage over alkylation of esters[13] and nitriles[14] assuming compatibility of the amide functionality in further synthetic operations.[15,16]

Experimental. Li-1a was generated using 1.1 equiv. LDA/Et_2O/0°C/1 h; alkylation was effected with 1.1 equiv. RX/0°C/4 h. diLi-1b and -3b were formed using 2.2 equiv. n-BuLi-TMEDA/THF/r.t./1 h and alkylations were carried out with 1.2 equiv. RX/r.t./2 h. The procedure for 3a was the same as for 1b except 1.1 equiv. of reagents were used. Cu-3a and diCu-3b were prepared using 1.0 equiv. and 2.0 equiv. n-BuLi-TMEDA respectively in THF/0°C→r.t./1 h. Cu_2I_2 (1.0 and 2.0 equiv. respectively) was added at -78°C and the mixture was stirred (1 h). 1.0 equiv. RX was injected and the solution was warmed to r.t. overnight. Standard work up procedure was followed.

References and Notes

1. R.B. Meyer and C.R. Hauser, J. Org. Chem., 26, 3696 (1961).
2. Review: E.M. Kaiser, J.D. Petty, and P.L.A. Knutson, Synthesis, 509 (1977). Recent work: P. Hullot, T. Cuvingny, M. Larcheveque, and H. Normant, Can. J. Chem., 55, 266 (1977) and refs. therein; P.G. Gassman and R.J. Balchunis, J. Org. Chem., 42, 3237 (1977) and refs. therein.
3. A. Wu and V. Snieckus, Tetrahedron Lett., 2057 (1975).
4. Dilithiated trans-β-methylcinnamanilide is, to our knowledge, the only simple unsaturated amide which has been previously studied: J.F. Wolfe, G.B. Trimitsis, and D.R. Morris, J. Org. Chem., 34, 3263 (1969).
5. D.M. von Schriltz, E.M. Kaiser, and C.R. Hauser, J. Org. Chem., 32, 2610 (1967).
6. a) J.A. Katzenellenbogen and A.L. Crumrine, J. Am. Chem. Soc., 98, 4925 (1976). See also b) B.S. Pitzele, J.S. Baran, and D.H. Steinman, Tetrahedron, 32, 1347 (1976).
7. Reaction conditions and observations were similar to those recorded in ref. 6a, i.e. yields were drastically reduced unless fresh n-BuLi was used and the reaction solution was yellow to golden brown rather than greyish in color.
8. We have been unsuccessful in effecting copper-mediated alkylation of 1a,b.
9. J.A. Katzenellenbogen and A.L. Crumrine, J. Am. Chem. Soc., 96, 5662 (1974).
10. For use of $LiAl(OEt)_2H_2$, see H.C. Brown and A. Tsukamoto, J. Am. Chem. Soc., 86, 1089 (1964).
11. For a recent synthesis, see M. Bertrand, G. Gil, and J. Viala, Tetrahedron Lett., 1785 (1977).
12. B.C. Challis and J. Challis in "The Chemistry of Amides," S. Patai and J. Zabicky, eds., Interscience Publ., New York, 1970, p. 731. For recent methods of amide modification, see P.G. Gassman, P.K.G. Hodgson, and R.J. Balchunis, J. Am. Chem. Soc., 98, 1275 (1976); H. Kuzuhara, O. Mori, and S. Emoto, Tetrahedron Lett., 379 (1976); J.C. Martin and J.A. Franz, J. Am. Chem. Soc., 97, 6137 (1975); F.M. Menger, J.U. Rhee, and H.K. Rhee, J. Org. Chem., 40, 3803 (1975); V. Gani and C. Lapinte, Tetrahedron Lett., 2775 (1973); I. Shahak and Y. Sasson, J. Am. Chem. Soc., 95, 3440 (1973).
13. J.L. Herrmann, G.R. Kieczykowski, and R.H. Schlessinger, Tetrahedron Lett., 2433 (1973) and refs. therein.
14. G.R. Kieczykowski, R.H. Schlessinger, and R.B. Sulsky, Tetrahedron Lett., 4647 (1975).
15. All new compounds exhibit spectroscopic and analytical data consistent with their assigned structures.
16. We are grateful to the National Research Council of Canada and Bristol Laboratories for financial support.