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TANDEM CONJUGATE ADDITION-α-ALKYLATION OF UNSATURATED AMIDES. SYNTHETIC METHODOLOGY.

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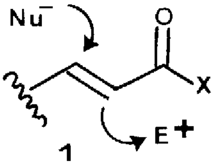
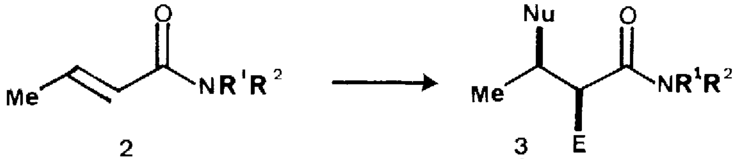
Summary: 1,4-Addition of RLi, RMgX, and $(RS)_2CHLi$ reagents to unsaturated amides 2a-c followed by α-alkylation is shown to constitute a general and efficient synthetic procedure for the formation of two C-C bonds in a single step.

A synthetically valuable modern perspective of the Michael reaction[1] accrues from cuprate 1,4-addition[2] to unsaturated carbonyl systems in tandem with α-alkylation (1) which results in the highly stereoselective formation of two new C-C bonds in a single operation.[3] With strong (RLi,RMgX) and weak $[(RS)_2CHLi]$ nucleophiles, this methodology loses distinction owing to competitive 1,4- and 1,2-addition.[4] Recent reports concerning the attainment of enhanced or exclusive 1,4-regiochemistry through HMPT solvent effects,[5] and charge-directed (1, X = $\bar{C}(PPh_3)CO_2R$)[6] and tetracarbonyliron complex[7] control protocols open further doors for synthetic application.



1

X = H,R,OR



2 3

a: $R^1 + R^2 = -(CH_2)_5-$; b: $R^1 = R^2 = Me$; c: $R^1 = H, R^2 = Me$

The conjugate addition reaction of unsaturated amides has received sporadic attention[8,9] which may explain its stunted evolution as a synthetic method.[10] Recently the general participation of unsaturated tertiary thioamides in the process 1, Nu⁻ = RMgX,RLi has been reported.[11] In this Letter, we demonstrate that unsaturated amides themselves are discrete and effective substrates for the tandem conjugate addition-α-alkylation reaction.[12,13] In the accompanying Letter,[14] we describe the application of this concept to the synthesis of 1-aryltetralin lignans.

Representative results of our studies on tertiary (2a-b) and secondary (2c) amides are given in the TABLE. That tertiary crotonamides, unlike analogous senecioamides,[13d] cannot be similarly deprotonated was indicated by early experiments on 2a involving treatment with LDA[15] or *t*-BuLi followed by alkylation (entries 1,2). To generalize, we found that alkyl and aryl lithium reagents undergo rapid Michael addition to tertiary crotonamides **2a** and **2b** and the resulting amide enolates are quenched with alkyl and allylic halides, $ClCO_2Et$, aromatic aldehydes, and $(PhS)_2$ to give α,β-dialkylated products **3** in good yield (entries 3,4,6-10). The enolate may act as a Michael donor to another molecule of crotonamide to give a glutaramide derivative (entry 11).[16] 1,4-Regioselective reaction with Grignard reagents proceeds at higher temperature and, as effectively, in the presence of HMPT (entries 5,12). The latter condition is obligatory for the successful reaction of **2b** with lithium enolates (entries 12,14). Potentially useful functionalized compounds are obtained by introduction of the 1,3-dithiane moiety (entries 15,16).[14]

Secondary crotonamide **2c** undergoes smooth conjugate addition of alkyllithium reagents (2 equiv.) to give, after *in situ* electrophilic trapping, saturated products (entries 17-19).[17,18]

Methodology developed here and elsewhere[11] attests to the broadly parallel behavior of tertiary β-monoalkylated unsaturated amides and thioamides in the fundamental process **1**; also to the considerable scope of this reaction.[18] Since thioamides are derived from amides, the advantage of using one functionality over the other may be largely determined by the nature of subsequent modifications. Failure of both substrates to react with cuprates and malonate anions constitutes synthetic limitations.[11,19] Furthermore, secondary unsaturated amides are Michael acceptors only for hard RLi nucleophiles.[12,19] The recent carbanionic chemistry of unsaturated amides[13] is providing a platform upon which new synthetic strategy may be forged.[20]

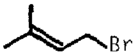
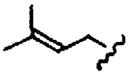
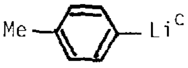
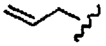
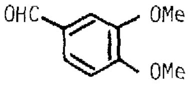
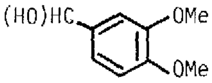
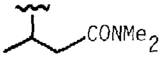
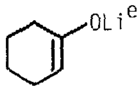
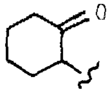
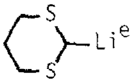
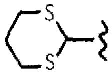
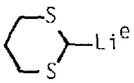
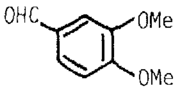
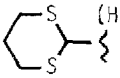
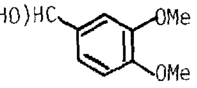
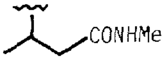
Typical Experimental Procedure

To a solution of 1,3-dithiane (6 mmol) in anhydrous THF (20 mL) at -70°C under nitrogen was added *n*-BuLi (6 mmol) and after 30 min, HMPT (9 mmol). The reaction was stirred for 20 min and then compound **2b** (6 mmol) in THF (5 mL) was added. The mixture was allowed to warm to ambient temperature over a 2.5 h period, cooled (-70°C), quenched with methyl iodide (9 mmol), and allowed to stir overnight. Extraction (CH_2Cl_2) followed by standard work up and chromatography (SiO_2, hexane-EtOAc) gave product (entry 15).

References and Footnotes

1. H.O. House, "Modern Synthetic Reactions," 2nd ed., W.A. Benjamin, Menlo Park, Calif., 1972, p. 595. M.E. Jung, *Tetrahedron*, **32**, 3 (1976).
2. G.H. Posner, *Org. Reactions*, **19**, 1 (1972).
3. Review: G.H. Posner, C.E. Whitten, J.J. Sterling, D.J. Brunelle, C.M. Lentz, A.W. Runquist, and A. Alexakis, *Ann. N.Y. Acad. Sci.*, **295**, 249 (1977). Recent applications: S. Danishefsky, K. Vaughan, R. Gadwood, and K. Tsuzuki, *J. Am. Chem. Soc.*, **102**, 4262 (1980); R. Davis and K.G. Untch, *J. Org. Chem.*, **44**, 3755 (1979); K.K. Heng and R.A.J. Smith, *Tetrahedron*, **35**, 425 (1979); W. Oppolzer, K. Battig, and M. Petrzilka, *Helv. Chim. Acta*, **61**, 1945 (1978); C.M. Lentz and G.H. Posner, *Tetrahedron Lett.*, 3769 (1978).
4. For a recent discussion of this problem, see N.-y. Wang, S.-s. Su, and L.-y. Tsai, *Tetrahedron Lett.*, 1121 (1979).
5. M. El-Bouz and L. Wartski, *Tetrahedron Lett.*, 2897 (1980) and refs. therein; F.E. Ziegler and C.C. Tam, *ibid.*, 4717 (1979).

TABLE Synthesis of α,β-Disubstituted Amides 3 from Crotonamides 2

Entry	Amide	Nu^-	E^+	Product[a]		Yield[b] %
				Nu	E	
1	2a	LDA	MeI	3a, $N(i\text{-}Pr)_2$	Me	71
2	2a	*t*-BuLi	*n*-PrBr	3a, *t*-Bu	*n*-Pr	85
3	2a	*n*-BuLi		3a, *n*-Bu		75
4	2a	 [c]	H^+	3a, 	H	55
5	2a	 [d]	MeI	3a, 	Me	65
6	2b	*n*-BuLi		3b, *n*-Bu		90
7	2b	*s*-BuLi	MeI	3b, *s*-Bu	Me	61
8	2b	*n*-BuLi		3b, *n*-Bu		86
9	2b	*n*-BuLi	$ClCO_2Et$	3b, *n*-Bu	CO_2Et	87
10	2b	*n*-BuLi	$(PhS)_2$	3b, *n*-Bu	PhS	65
11	2b	*n*-BuLi		3b, *n*-Bu		85
12	2b	PhMgBr[e]	H^+	3b, Ph	H	50
13	2b	$PhC(OLi)=CH_2$[e]	H^+	3b, $PhCOCH_2$	H	72
14	2b	 [e]	H^+	3b, 	H	60
15	2b	 [e]	MeI	3b, 	Me	75
16	2b	 [e]		3b, 		80
17	2c	*n*-BuLi	H^+	3c, *n*-Bu	H	97
18	2c	*n*-BuLi	MeI	3c, *n*-Bu	Me	70
19	2c	*n*-BuLi		3c, *n*-Bu		48[f]

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[a] All products show analytical and spectral (IR,NMR,MS) data consistent with the assigned structures. Products with two chiral centers were obtained as diasteriomeric mixtures. [b] Unoptimized yields. [c] Prepared by metal-halogen exchange at -100°C. [d] Added at -20°C. [e] Added HMPT (1-1.5 equiv.). [f] Based on 2c.

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9. RMgX reagents: a) J. Klein, Tetrahedron, **20**, 465 (1964); b) G. Daviaud and P. Miginiac, Tetrahedron Lett., 3251 (1971); RLi reagents; c) G. Gilbert and F. Aycock, J. Org. Chem., **22**, 1013 (1957); R_2CuLi reagents (1,6-addition to diene amides): d) G. Daviaud and P. Miginiac, Tetrahedron Lett., 3345 (1973); CH_2= $SOMe_2$; e) H. König, H. Metzger, and K. Seelert, Chem. Ber., **98**, 3712 (1966).
10. See, however, J.L. Herrmann, J.E. Richman, and R.H. Schlessinger, Tetrahedron Lett., 2599 (1973); G. Stork and A.G. Schultz, J. Am. Chem. Soc., **93**, 4074 (1971).
11. a) Y. Tamaru, T. Harada and Z. Yoshida, J. Am. Chem. Soc., **101**, 1316 (1979); b) Y. Tamaru, T. Harada, H. Iwamoto, and Z. Yoshida, ibid., **100**, 5221 (1978).
12. During the preparation of this Letter, we learned of similar work [J.E. Baldwin and W.A. Dupont, Tetrahedron Lett., 1881 (1980)] dealing with 1,4-addition of RLi reagents to N-phenylacrylamides. In order to avoid overlap and indicate the broad scope of the reaction, we have included only a few complementary examples of secondary amides and stressed tertiary amides and Michael donors which were not investigated by these workers.
13. For other uses of metalated unsaturated amide synthons, see a) P. Beak and D.J. Kempf, J. Am. Chem. Soc., **102**, 4550 (1980); b) W.R. Baker and R.M. Coates, J. Org. Chem., **44**, 1022 (1979); c) R.R. Schmidt, J. Talbiersky, and P. Russegger, Tetrahedron Lett., 4273 (1979); d) J.A. Oakleaf, M.T. Thomas, A. Wu and V. Snieckus, ibid., 1645 (1978) and refs. therein
14. G.B. Mpango and V. Snieckus, Tetrahedron Lett., following communication in this issue.
15. For LDA addition to unsaturated esters, see J.L. Herrmann, G.R. Kieczykowski and R.H. Schlessinger, Tetrahedron Lett., 2433 (1973); C.C. Shen and C. Ainsworth, ibid., 89 (1979).
16. Products of this type compromise the yields of **3** if α-alkylation is slow or not carried out within a specified time (see also refs. 8, 9e, 11b and TABLE, entry 19).
17. As noted by Baldwin and Dupont (ref. 12) and inadvertently observed by others (refs. 9a, 9e), this constitutes a charge-directed conjugate addition first conceptualized by Cooke (ref. 6).
18. Michael addition is not observed for β,β-dialkylated tertiary (refs. 12,13d) and α-alkylated secondary (ref. 13a) unsaturated amides.
19. **2b** and **2c** are unreactive towards Me_2CuLi and $NaC(CO_2R)_2$ under the standard conditions; **2c** is also unreactive towards PhMgBr.
20. We thank A. Wu for initial observations, the Natural Sciences and Engineering Research Council of Canada for financial support, and Jadavpur University for a leave of absence to K.K.M.

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