

Table I. Cycloadditions of Ynamines with α,β -Unsaturated Sulfones

sulfone 2	ynamine 3	% yield of adduct 4	% yield of ketone 7	mp, ^a °C
phenyl vinyl sulfone (2a)	3a	95	84	65-70 ^b
phenyl (<i>E</i>)- β -styryl sulfone (2b)	3a	60 ^c		
benzothiophene 1,1-dioxide (2d)	3a	100 ^d	95	131-133
(<i>E</i>)-(methoxycarbonyl)ethenyl phenyl sulfone (2c)	3a	100 ^{d,e}		
2-sulfolene (2e)	3a	35 ^f		
phenyl 1-propynyl sulfone (2f)	3a	100 ^{d,e}		
1,3-butadien-1-yl phenyl sulfone (5)	3a	90-100	72	82-85
phenyl vinyl sulfone (2a)	3b	75	64	(oil) ^g

^a The cycloadducts 4 were characterized by ¹H NMR, IR, and MS; the isolated ketones gave satisfactory spectral and elemental analyses. ^b A cis-trans mixture of 7 results. ^c At 100 °C cycloaddition and ring opening of 4 occurred. ^d By NMR analysis no starting sulfone was discernible after reaction. ^e Cycloaddition occurs exothermically at 25 °C, but attempted hydrolysis to 7 took an undetermined course. ^f Cycloaddition and isomerization to 3-sulfolene were competitive above 60 °C. ^g This product was purified by column chromatography.

ture of 1.0 g (5 mmol) of sulfone 5, either dissolved in 10 mL of methylene chloride or neat, with 0.97 mL (7 mmol) of ynamine 3a led to an exotherm after a few minutes. After standing several h, the solvent and excess ynamine were removed in vacuo at 50 °C and 0.1 mmHg. For the neat reaction the starting sulfone was consumed; in CH₂Cl₂ medium, 10% of 5 remained. When acetonitrile was used as a solvent, 40% of 5 was unconsumed. Product 6: ¹H NMR (CDCl₃) δ 1.06 (6 H, m, *J* = 7 Hz), 1.62 (3 H, sl br), 2.25-2.6 (2 H, m), 2.85 (4 H, g, *J* = 7 Hz), 3.30 (1 H, m), 6.46 (1 H, d, *J* = 15 Hz), 7.1 (1 H, d of d, *J* = 8, 15 Hz), 7.66 (3 H, m), 7.9 (2 H, m); IR (neat) sharp, intense absorptions at 1605 and 1660 cm⁻¹.

Hydrolysis of product 6 from a 30-mmol run was carried out in 30 mL of ether with 3 mL of concentrated HCl for 1 h. The ether layer was washed with water, dried with anhydrous MgSO₄, and evaporated to yield isomers of 9; column chromatography on silica gel and elution with an ether-hexane pair (1:1) gave a colorless solid, which was recrystallized from methanol to give one isomer of 9, mp 82-85 °C, presumably having the C=O and SO₂Ph groups *E*: ¹H NMR (CDCl₃) δ 2.02 (2 H, d, *J* = 7 Hz), 2.59 (1 H, m), 3.0-4.2 (2 H, m), 4.46 (2 H, d, *J* = 7 Hz), 6.56 (1 H, m), 7.8-8.3 (5 H, m); IR (mineral oil) 1750 (C=O), 1680 (C=C) cm⁻¹.

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(10) Sulfone 5 was prepared from 1,3-butadiene in three steps: (a) 1,3-butadiene and PhSO₂Cl at -78 °C in CH₂Cl₂ with CuCl and Et₃NHCl yielded 1-chloro-4-(phenylsulfonyl)-2-butene; (b) treatment of the chloro compound with Et₃N and Me₂NH provided 1-amino-4-(phenylsulfonyl)-2-butene, which was a convenient, storable source of 5; (c) quaternization of the amino compound with MeI in MeOH and treatment of the resulting quaternary salt with aqueous NaOH liberate 5.

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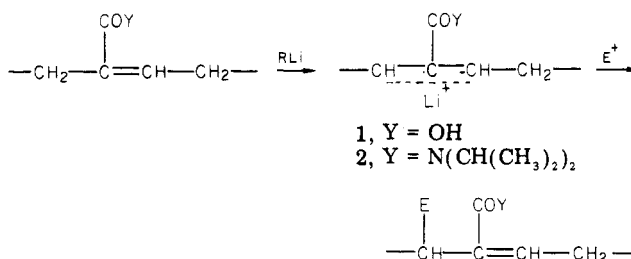
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β' Metalation of α,β -Unsaturated Tertiary Amides

Summary: Novel β' metalations of the α,β -unsaturated tertiary amides *N,N*-diisopropyl-1-cyclohexenecarboxamide (3), (*E*)-*N,N*-diisopropyl-2-methyl-2-butenamide (7), and *N,N*-diisopropyl-6-(trimethylsilyl)-1-cyclohexenecarboxamide (10) are reported. Additions of the β' -lithio- α,β -unsaturated tertiary amides 4, 8, and 11 to a

variety of electrophiles, including in the case of 8 subsequent formation of five-membered rings, illustrate the value of this approach for achieving substitution at the β' position of α,β -unsaturated carboxylic acid derivatives.

Sir: Recent communications which report that α,β -unsaturated secondary amides and thioamides react with 2 equiv of alkylolithiums to give a species which is dilithiated at the nitrogen and β' -carbon provide the basis for a new approach to β' substitution of α,β -unsaturated carboxylic acid derivatives.^{1,2} In view of the interest in the novel β' -lithiomethacrylate synthon 1, we now communicate our observation that diisopropyl tertiary amides bearing potentially acidic β - and γ -hydrogens undergo β' metalation at low temperatures to give stable β' -lithio- α,β -unsaturated amides 2 which can subsequently react with a variety of electrophiles.³



Addition of *N,N*-diisopropyl-1-cyclohexenecarboxamide (3) to 1.1 equiv of *sec*-butyllithium-tetramethylethylenediamine in tetrahydrofuran at -78 °C followed by addition of an electrophile leads to β' -substituted amides 5 via the substituted allyllithium 4. As shown in Table I, deuteration, alkylation, silylation, sulfenylation, oxidation, and condensation with carbonyl compounds proceed in useful yields. Products resulting from β - or γ -hydrogen removal are not observed; however, reaction of 4 with dimethylformamide gives the conjugated product 6 in which isomerization of the double bond has occurred. A typical experimental description is given at the end of this report.

(1) For cases in which potentially acidic β - and γ -hydrogens are present, see: (a) Beak, P.; Kempf, D. J. *J. Am. Chem. Soc.* 1980, 102, 4550. (b) Tamaru, Y.; Kagotani, M.; Yoshida, Z. *Tetrahedron Lett.* 1981, 3409. (c) Tamaru, Y.; Kagotani, M.; Furukawa, Y.; Amino, Y.; Yoshida, Z. *Ibid.* 1981, 3413. For cases in which only β -hydrogens are present, see: (a) Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* 1980, 45, 4257. (b) Tanaka, K.; Nozaki, Y.; Tamura, N.; Tanikaga, R.; Kaji, A. *Chem. Lett.* 1980, 1567.

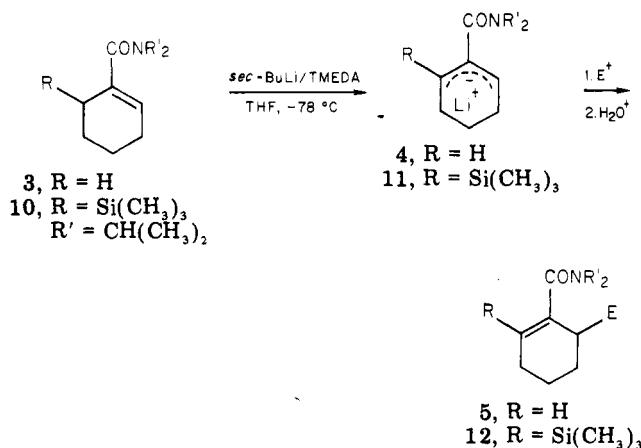
(2) For β' -carbanionic methacrylic acid synthons, see: (a) Löffler, A.; Pratt, R. D.; Pucknat, J.; Gelbard, G.; Dreiding, A. S. *Chimia* 1969, 23, 413. (b) Hegedus, L. S.; Wagner, S. D.; Waterman, E. L.; Siirala-Hansen, K. *J. Org. Chem.* 1975, 40, 593. (c) Carlson, R. M.; Oyler, A. R. *Ibid.* 1976, 41, 4065. (d) Carlson, R. M. *Tetrahedron Lett.* 1978, 111.

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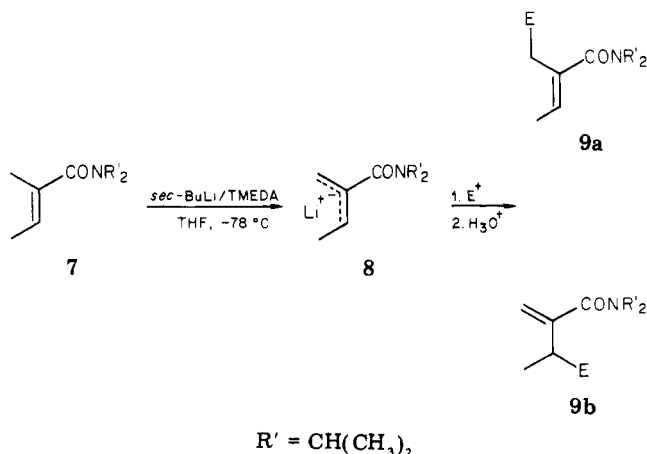
Table I. Lithiation and Electrophilic Substitution of 3, 7, and 10

amide	electrophile	product	% yield ^a
3	D ₂ O	5, E = D	85 (97% d ₁)
3	C ₆ H ₅ CH ₂ Cl	5, E = CH ₂ C ₆ H ₅	58
3	C ₆ H ₅ I	5, E = C ₆ H ₅	68
3	CH ₃ (CH ₂) ₅ Br	5, E = (CH ₂) ₅ CH ₃	56
3	Cl(CH ₂) ₃ Br	5, E = (CH ₂) ₃ Cl	63
3	(C ₆ H ₅) ₂ CO	5, E = COH(C ₆ H ₅) ₂	61
3	(CH ₃) ₃ SiCl	10	57
3	(C ₆ H ₅) ₂ S	5, E = SC ₆ H ₅	56
3	B(OCH ₃) ₃ ; H ₂ O ₂ , HOAc	5, E = OH	66
3	HCON(CH ₃) ₂	6	42
7	D ₂ O	9a,b, E = D	93 ^{b-d} (95% d ₁)
7	(C ₆ H ₅) ₂ N	9a,b, E = C ₆ H ₅ NNHC ₆ H ₅	75 ^e
7	(C ₆ H ₅) ₂ CO	9a,b, E = COH(C ₆ H ₅) ₂	82 ^f
7	(CH ₃) ₂ CO	9a,b, E = COH(CH ₃) ₂	81 ^g
7	CH ₃ (CH ₂) ₅ I	9a, E = (CH ₂) ₅ CH ₃	63 ^h
7	(CH ₃) ₃ SiCl	9a, E = Si(CH ₃) ₃	58 ^{c,h}
7	(C ₆ H ₅) ₂ S	9a, E = SC ₆ H ₅	67 ^{h,i}
10	C ₆ H ₅ I	12, E = C ₆ H ₅	65
10	C ₆ H ₅ CH ₂ Cl	12, E = CH ₂ C ₆ H ₅	81
10	(CH ₃) ₂ CO	12, E = COH(CH ₃) ₂	73
10	(C ₆ H ₅) ₂ CO	12, E = COH(C ₆ H ₅) ₂	90
10	C ₆ H ₅ CON(CH ₃) ₂	12, E = COC ₆ H ₅	73
10	C ₆ H ₅ CHO	13, 14	16, 44

^a Analytically pure material. ^b 87:13; **9a**, **9b**. ^c Lithiation at -96 °C. ^d Lithiation at -78 °C gave 82% (97% d₁) **9a**, **9b**; 86:14. ^e 39:61, **9a**, **9b**. ^f 46:54; **9a**, **9b**. ^g 60:40; **9a**, **9b**. ^h Less than 5% of the isomer **9b** is present. ⁱ Obtained as a mixture of *E* and *Z* isomers. The ratio varies and is attributed to base-catalyzed isomerization.



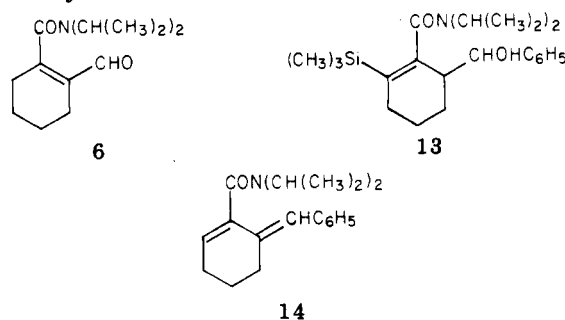
Similarly, the acyclic tertiary amide (*E*)-*N,N*-diisopropyl-2-methyl-2-butenamide (**7**) undergoes selective β metalation upon addition to *sec*-butyllithium-tetramethylethylenediamine at -78 °C to give the unsymmetrically substituted allyllithium **8**. In this case two re-



gioisomers are possible on reaction of **8** with electrophiles. As shown in Table I, **9a** and **9b** are observed on deuteration and additions to multiple bonds, while a ratio of

greater than 95:5 **9a:9b** is observed on alkylation, silylation, and sulfenylation.

Regiochemical control of the substitution site is observed in the reactions of the silylated tertiary amide **10**. The intermediate **11** is trapped with alkyl halides, ketones, and *N,N*-dimethylbenzamide exclusively γ to silicon to give **12**.⁴ Reaction with benzaldehyde, however, gives a mixture of **13** and diene **14** in 16% and 44% yields, respectively; the latter presumably results from trapping α to silicon followed by elimination.^{4d,5}



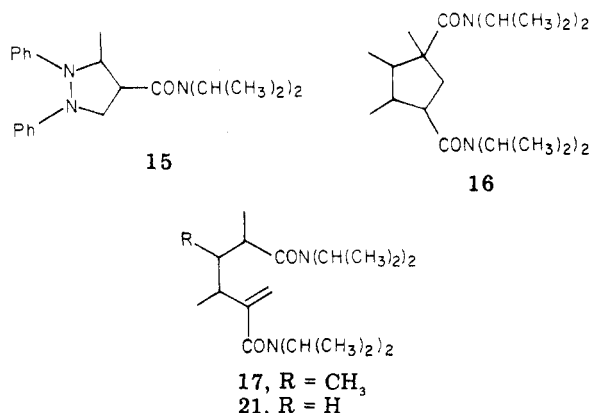
A particular advantage of the tertiary amide for the synthon **1** is its potential for activating anionic cyclization after addition to an appropriate electrophile.^{3,6} Such a ring formation has been observed by Kaufmann et al.⁶ for reaction of the transient β' -lithio- α,β -unsaturated tertiary amide from *N,N*-diisopropyl-2-methylpropanamide (**18**) with itself and with azobenzene. An analogous process is

(4) This selectivity is typical of silyl-substituted allyllithiums: (a) Corriu, R. J. P.; Masse, J. *J. Organometal. Chem.* **1973**, *57*, C5. (b) Corriu, R. J. P.; Masse, J.; Samate, D. *Ibid.* **1975**, *93*, 71. (c) Corriu, R. J. P.; Lanneau, G. F.; Leclercq, D.; Samate, D. *Ibid.* **1978**, *144*, 155. (d) Lau, P. W. K.; Chan, T. H. *Tetrahedron Lett.* **1978**, 2383.

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(6) For studies of the additions of allyl anions to olefins, see: (a) Luteri, G. F.; Ford, W. T. *J. Org. Chem.* **1977**, *42*, 820; *J. Am. Chem. Soc.* **1977**, *99*, 5330. (b) Eidenschink, R.; Kauffmann, T. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 292. (c) Boche, G.; Martens, D. *Ibid.* **1972**, *11*, 724.

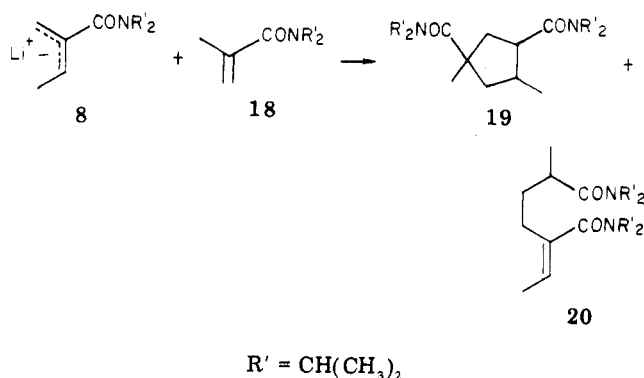
demonstrated by conversion of **9b**, obtained from **8** and azobenzene, to the dihydropyrazoline **15** in 22% yield and by the formation of **16**, in 72% yield, when a THF solution of **7** and 0.55 equiv of *sec*-butyllithium-tetramethylethylenediamine is allowed to warm to ambient temperature prior to quenching.⁷ If the latter reaction is quenched at -78 °C, the acyclic amide **17**, the anion of which presumably is the precursor to **16**, is obtained in 40% yield.⁷



Of greater interest is the addition of the anion **8** to **18** at -60 °C followed by warming to ambient temperature to give the cyclopentane derivative **19** in 59% yield along with a 16% yield of **20**.⁷ If this reaction is quenched at -65 °C **21** is obtained in 60% yield.⁷ This result, which establishes that the β' -lithio- α,β -unsaturated amides can be used in an addition-cyclization sequence, has important synthetic potential and its generalization is under further investigation.

This facile preparation of the novel β' -lithiomethacrylate synthon **1**, along with the classic enolate and addition chemistry well-known for this system under other basic conditions,⁸ appears to substantially expand the possibilities for controlled syntheses with α,β -unsaturated carboxylic acid derivatives. For the β' metalations of secondary amides it was suggested^{1,2} that additions and enolate formation were suppressed by initial proton removal from the nitrogen. The present results indicate that such deactivation at both the carbonyl and β positions can be accomplished through steric inhibition.⁹ The implication of these results, that the tertiary amide is effective in directing metalation due to strong complexation with lithium, is consistent with the paramount position of this group as a director of aromatic lithiation¹⁰ and with metalations similarly directed in allyl systems by the ionized secondary amide,¹ alkoxide,^{2c,11} and the neutral dimethylamino¹² groups.

Conversion of 3 to 5. A stirred solution of *sec*-butyllithium (1.0 mL, 1.3 mmol) and *N,N,N',N'*-tetramethylethylenediamine (0.2 mL, 1.3 mmol) in 5 mL of tetrahydrofuran was cooled in a dry ice/acetone bath and treated dropwise with 269 mg (1.29 mmol) of **3** in 5 mL of tetrahydrofuran. The resulting red-orange solution was stirred under N₂ for 5 min, treated with 0.2 mL (1.7 mmol)



of benzyl chloride, and allowed to warm to ambient temperature. Extractive workup followed by separation by medium-pressure liquid chromatography and bulb-to-bulb distillation yielded 225 mg (58%) of pure **5** (E = CH₂C₆H₅): ¹H NMR (360 MHz) δ (CDCl₃) 1.1-1.6 (m, br d, 15 H), 1.63-1.71 (m, 1 H), 2.07-2.10 (m, 2 H), 2.29 (t, *J* = 12.4 Hz, 1 H), 2.76 (m, 1 H), 2.96 (d of d, *J* = 13.1, 3.3 Hz, 1 H), 3.3-3.5 (br d, 1 H), 4.2-4.4 (br d, 1 H), 5.73 (m, 1 H), 7.17-7.19 (m, 3 H), 7.25-7.28 (m, 2 H); IR (NaCl, film) 2940 (m), 1620 (s), 1435 (s), 1372 (s), 1325 (s) cm⁻¹; mass spectrum (70 eV), *m/e* (relative intensity) 299 (20.6), 256 (9.4), 208 (100) 199 (48.5), 198 (25.0), 91 (46.7), 43 (28.6), 41 (21.1). anal. Calcd for C₂₀H₂₉NO: C, 80.22; H, 9.76; N, 4.68. Found: C, 79.91; H, 9.75; N, 4.79.

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Macrolide Synthesis: Narbonolide

Summary: Narbonolide, a 14-membered polyoxomacrolide, has been synthesized through two major steps: (i) condensation of the C₁-C₁₀ and C₁₁-C₁₅ fragments and (ii) macrolactonization using a phosphoric acid mixed anhydride intermediate.

Sir: Narbonolide (**1**),¹ isolated from fermentation broths of *Streptococcus venezuelae* MCRL 0376, is a metabolic intermediate leading to narbomycin (**2**)² and pikromycin (**3**),³ both of which belong to the well-known family of 14-membered polyoxomacrolides.⁴ The full stereostructures of narbonolide and narbomycin, which apparently

(7) The compounds **16**, **17**, **19**, and **21** are obtained as mixtures of diastereomers which are separated by medium-pressure liquid chromatography.

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