Reductive Alkylation of γ-Cyano-α,β-unsaturated Ketones. A Modified Robinson Annulation Process to α,α-Disubstituted-β,γ-unsaturated Cyclohexanone System

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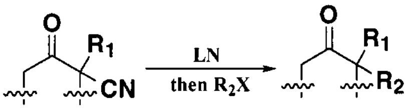
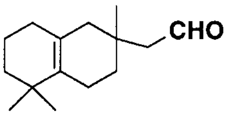
Abstract: Reductive alkylation of various 4-cyano-2-cyclohexenones, readily available from α-cyano ketones via a Robinson annulation process, gave rise to the corresponding 2,2-disubstituted-3-cyclohexenone derivatives in a completely regioselective manner. Application of this methodology resulted in an efficient synthesis of the marine natural product nanaimoal in racemic form.

Key words: ketones, cyano compounds, reduction, alkylation

It was recently discovered in our laboratories that α-cyano ketones undergo facile reductive alkylation upon sequential treatment with lithium naphthalenide (LN) and an alkylating agent (Scheme 1).[1] As a result of this finding, it became of interest to explore the reductive alkylation of vinylogous α-cyano ketones. The preliminary experimental results disclosed in this paper showed that the reductive alkylation is highly efficient and completely regioselective with the alkylation occurring specifically at the α-carbon with simultaneous transposition of the double bond towards the γ-carbon. In essence, this methodology allows the expeditious formation of a quaternary center bearing a vinyl group. Such a system is found in a wide variety of naturally occurring compounds (e.g. nanaimoal (**1**)[2]) and is not readily accessible by existing methods.



Scheme 1



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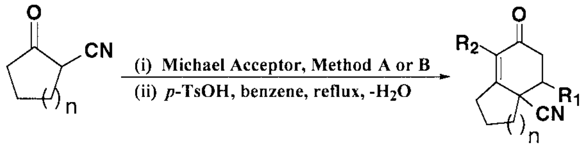
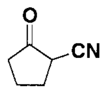
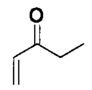
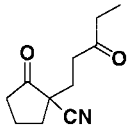
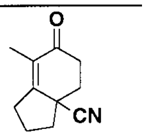
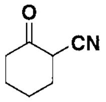
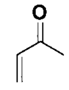
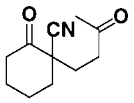
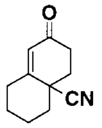
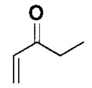
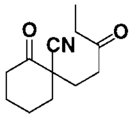
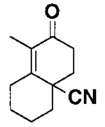
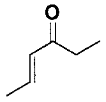
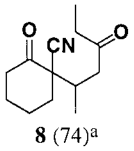
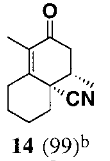
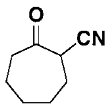
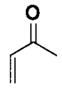
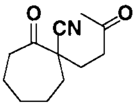
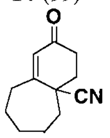
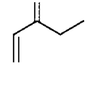
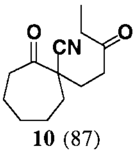
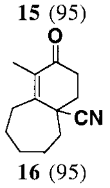
A series of γ-cyano-α,β-unsaturated ketones was readily prepared via Robinson annulation of α-cyano ketones **2-4**.[3] The Robinson annulation was found to be most effective when carried out in two separate operations: Michael addition followed by aldol condensation. The Michael process, which is facilitated by the presence of the doubly activated methylene group in the Michael donor, could be effected by two different methods. In one method (method A) aluminum oxide[4] was used as the reagent. In a typical experiment, the α-cyano ketone was added to activated (100 °C, 4 h) aluminum oxide at room temperature followed by dropwise addition of the Michael acceptor. This reaction has the advantage of being rapid (20 min) and easy to workup (dilution with ether followed by filtration). However, neither α-cyanocyclopentanone (**2**) nor β-substituted methyl vinyl ketone derivatives was amenable to this reaction. A more universal procedure (method B) involves the treatment of a dimethoxyethane (DME) solution of α-cyano ketones with a Michael acceptor in the presence of 1,4-diaza[2.2.2]bicyclooctane (DABCO).[5] Subsequent to the Michael addition, the adducts **5-10**[6] were individually treated with *p*-toluenesulfonic acid (1 eq) in refluxing benzene with azeotropic removal of water to effect the aldol condensation, giving bicyclic enones **11-16** in good yields. These results are compiled in Table 1.

Each of the Robinson annulation products was subjected to reductive alkylation with LN in THF[7]. A variety of alkylating agents were used (Table 2). The reductive removal of the cyano group was found to be rapid (30 min) even at -78 °C. In general, the subsequent alkylation also occurred smoothly, giving rise to the expected product in good yield (Entries 1-7) within a day at -78 °C. As a typical example, at -78 °C, a 0.98 M solution of LN (3 eq) in THF was added dropwise to a solution of cyano enone **13** in THF (ca. 0.5 mmol/mL) under a nitrogen atmosphere. After 30 minutes at -78 °C, benzyl bromide (3 eq) was introduced. The resulting solution was stirred at -78 °C for 20 h at which time saturated aqueous ammonium chloride was added. Extraction with ether followed by standard workup of the extracts and flash chromatography (silica gel; EtOAc:hexanes (1:400)) gave the desired product **17**[6] in virtually quantitative yield. This procedure applies well to all the α-substituted cyano enones studied (Entries 1-7). However, when the unsubstituted enone **15** was applied, the expected mono alkylated product **28** was not formed cleanly. Instead, a mixture consisting of the mono-, di-, and unalkylated products **28**, **24**, and **29** (ca. 3:2:8) was

Table 1 Robinson Annulation of Various α-Cyano Ketones

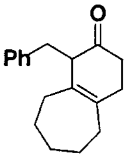


α-Cyano Ketone	Michael Acceptor	Method	Michael Adduct (% Yield)	Bicyclic Enone (% Yield)
 **2**		B	 **5** (87)	 **11** (83)
 **3**		A	 **6** (90)	 **12** (95)
3		A	 **7** (90)	 **13** (99)
3		B	 **8** (74)[a]	 **14** (99)[b]
 **4**		A	 **9** (89)	 **15** (95)
4		A	 **10** (87)	 **16** (95)

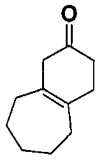
[a] A separable diastereomeric mixture of the Michael adduct was obtained in a 1:1 ratio. The yield refers to that of the mixture.

[b] The other diastereomer also gave identical results in the aldol condensation reaction.

produced. Apparently, under the reaction conditions, dialkylation at the expense of the mono-alkylated product occurred as a result of a proton transfer process between the originally formed enolate and the mono-alkylated product **28**. As a consequence of this observation, a procedure to facilitate dialkylation was developed. Thus, sequential treatment of compound **15** with 4 eq of LN at -78 °C and 4 eq of benzyl bromide at room temperature gave ketone **24** as the sole product (Table 2, Entry 8). This procedure proved to be general for direct dialkylation of several other cases (Entries 9-11), giving the dialkylation products **25-27** in synthetically useful yields.



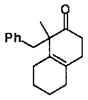
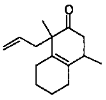
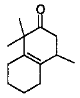
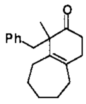
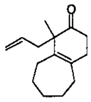
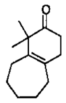
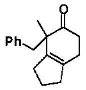
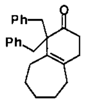
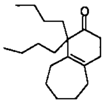
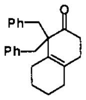
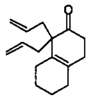
28



29

The experimental results described above demonstrate that reductive alkylation of γ-cyano-α,β-unsaturated ketones facilitates the formation of α,α-disubstituted-β,γ-unsaturated ketones in a completely regioselective manner. Both symmetrical and unsymmetrical substitution patterns can be achieved. The current work represents a modified Robinson annulation process which allows the expeditious formation of α,α-disubstituted-β,γ-unsaturated cyclohexanones which cannot be effectively prepared

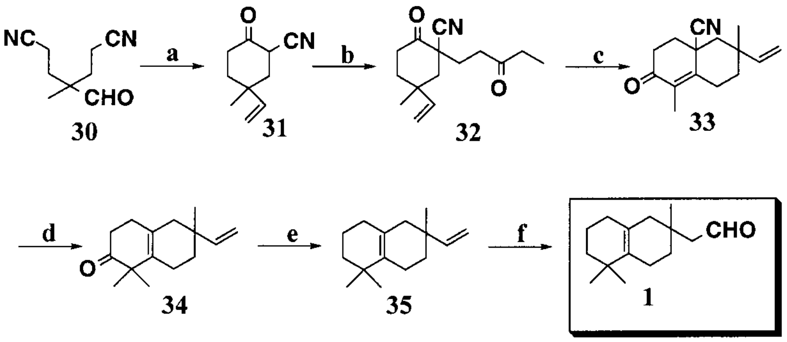
Table 2 Reductive Alkylation of γ-Cyano-α,β-unsaturated Enones

Entry	Substrate	Method[a]	Alkylating Agent	Time (hr)	Product	Yield(%)
1	**13**	**A**	Benzyl bromide	20	 **17**	99
2	**14**	**A**	Allyl bromide	19	 **18**	82[b]
3	**14**	**A**	Methyl iodide	19	 **19**	81
4	**16**	**A**	Benzyl bromide	24	 **20**	99
5	**16**	**A**	Allyl bromide	20	 **21**	87
6	**16**	**A**	Methyl iodide	24	 **22**	93
7	**11**	**A**	Benzyl bromide	22	 **23**	82
8	**15**	**B**	Benzyl bromide	20	 **24**	67
9	**15**	**B**	*n*-Butyl iodide	19	 **25**	63
10	**12**	**B**	Benzyl bromide	21	 **26**	81
11	**12**	**B**	Allyl bromide	24	 **27**	51

[a] **A**: LN (3 eq), -78 °C, 30 min, then alkylating agent (4 eq), -78 °C; **B**: LN (4 eq), -78 °C, 30 min, then alkylating agent (4 eq), r.t.

[b] An inseparable mixture of diastereomers was obtained in a ratio of 10 : 1. The relative stereochemistry of the products remains to be ascertained.

by Robinson annulation. This modified process is expected to find broad synthetic utility, especially towards the synthesis of various natural products containing a quaternary center bearing a vinyl group. An application is demonstrated in the total synthesis, in racemic form, of nanaimoal (**1**) (Scheme 2), a marine natural product isolated from the dorid nudibranch *Acanthodoris nanaimoensis*.[2]



a: i) $(C_6H_5)_3PCH_3Br$, *n*-BuLi, THF, -78°C to r.t., 30 min; ii) 2.48*N* $HCl_{(aq)}$, 17 h, 96%; **b**: DABCO, EVK, DME, 0°C to r.t., 23 h, 74%; **c**: *p*-TsOH, benzene, $-H_2O$, 2 h, 88%; **d**: LN, THF, -78°C, 45 min; then CH_3I, -78°C, 20 h, 77%; **e**: H_2NNH_2, KOH, DEG, 110-120 °C, 2 h; then 210-220°C, 4 h, 76%; **f**: i) Sia_2BH, THF, 0 °C to r.t., 25 h; ii) PCC, CH_2Cl_2, reflux, 3 h, 66%.

Scheme 2

Dicyano aldehyde **30**[8] was subjected to Wittig reaction with methylenetriphenylphosphorane in THF at a temperature range of -78 °C - 20 °C over a period of 30 min. Interestingly, under the reaction conditions, the Thorpe-Ziegler reaction occurred simultaneously to give a 96% yield of the desired cyano ketone **31**[9] after acid hydrolysis. Subsequent addition of ethyl vinyl ketone (EVK) (**31**→**32**) in the presence of DABCO followed by acid catalyzed aldol condensation resulted in the formation of cyano enone **33** in 65% yield. Reductive alkylation of **33** with LN and methyl iodide gave ketone **34** in 77% yield. The ketone carbonyl was subsequently removed by Wolff-Kishner reduction and the diene **35** thus obtained in 76% yield was subjected to hydroboration with disiamylborane and oxidation with pyridinium chlorochromate (PCC)[10] to give (±)-nanaimoal (**1**)[11] (66% yield) whose spectroscopic data were found to be in good agreement with those reported in the literature.[2]

Acknowledgement

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References and Notes

(1) Liu, H. J.; Zhu, J. L.; Shia, K. S. *Tetrahedron Lett.* **1998**, *39*, 4183.

(2) Ayer, S. W.; Hellou, J.; Tischler, M.; Andersen, R. J. *Tetrahedron Lett.* **1984**, *25*, 141.

(3) These compounds were readily prepared by Thorpe-Ziegler reaction of the corresponding alkanedicarbonitrile.

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(5) Liu, H. J.; Wynn, H. *Can. J. Chem.* **1986**, *64*, 649. Liu, H. J.; Wynn, H. *Can. J. Chem.* **1986**, *64*, 658.

(6) Satisfactory spectral and elemental or HRMS analytical data were obtained for all new compounds. Compound **13**: IR (neat): 2229 (CN), 1676 (C=O), 1622 cm^{-1} (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ 2.77 (dt, J_1 = 16 Hz, J_2 = 4 Hz, 1H), 2.54 (dd, J_1 = 16 Hz, J_2 = 4 Hz, 1H), 2.41 (dt, J_1 = 16 Hz, J_2 = 4 Hz, 1H), 2.25 (dt, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 2.10 (dm, J_1 = 12 Hz, 2H), 1.88 (m, 1H), 1.87 (dd, J_1 = 16 Hz, J_2 = 4 Hz, 1H), 1.74 (m, 2H), 1.70 (s, 3H), 1.40 (m, 1H), 1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0 (C=O), 150.1 (C=), 131.8 (C=), 120.6 (CN), 38.9 (CH_2), 34.0 (CH_2), 33.1 (CH_2), 28.4 (CH_2), 25.4 (CH_2), 22.3 (CH_2), 10.8 (CH_3); HRMS M^+: 189.1163 (calcd. for $C_{12}H_{15}NO$: 189.1154). Compound **17**: IR (neat): 1707 (C=O), 1601 cm^{-1} (C=C); ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (m, 3H), 6.95 (dd, J_1 = 8 Hz, J_2 = 1 Hz, 2H), 3.06 (d, J = 16 Hz, 1H), 2.72 (d, J = 16 Hz, 1H), 2.25 (ddd, J_1 = 16 Hz, J_2 = 9 Hz, J_3 = 7 Hz, 1H), 2.08 (m, 2H), 2.04 (dt, J_1 = 16 Hz, J_2 = 5 Hz, 1H), 1.87 (m, 2H), 1.81 (dm, J = 16 Hz, 1H), 1.39-1.75 (m, 5H), 1.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.8 (C=O), 138.1 (C=), 131.2 (C=), 130.4 (C=), 129.8 (CH=), 127.5 (CH=), 126.1 (CH=), 53.0 (C), 43.3 (CH_2), 37.6 (CH_2), 30.7 (CH_2), 28.6 (CH_2), 24.5 (CH_2), 23.6 (CH_3), 22.6(CH_2), 22.5 (CH_2); HRMS M^+: 254.1669 (calcd. for $C_{18}H_{22}O$: 254.1671).

(7) For the preparation of a stock solution of LN in THF, see Liu, H. J.; Shang, X. *Tetrahedron Lett.* **1998**, *39*, 367.

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(9) Diastereomeric mixtures were obtained for compounds **31**, **32**, and **33**.

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(11) For previous syntheses of **1**, see: Yamada, T.; Takabe, K. *Chem. Lett.* **1993**, 29. Omodani, T.; Shishido, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2781. Engler, T. A.; Ali, M. H.; Takusagawa, F. *J. Org. Chem.* **1996**, *61*, 8456. Ref. 2.

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