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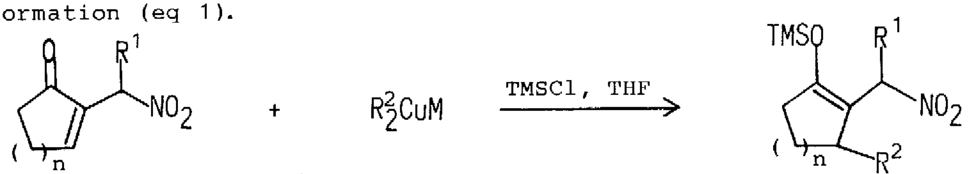
Me_3SiCl PROMOTED CONJUGATE ADDITION OF ORGANOCUPRATES TO BASE-SENSITIVE CYCLIC α-(NITROALKYL)ENONES

Rui Tamura,*[a] Shinobu Tamai,[b] Hitoshi Katayama[b] and Hitomi Suzuki[b]
[a]Department of Chemistry, Faculty of General Education, Ehime University
Matusyama 790, Japan
[b]Department of Chemistry, Faculty of Science, Ehime University
Matsuyama 790, Japan

Summary: α-(Nitroalkyl)enones undergo mono β-conjugate addition of organocuprates in the presence of TMSCl to provide the corresponding silyl enol ethers in good to excellent yield, despite the presence of the acidic α-nitro protons.

Allylic nitro compounds have become readily available[1] and proved to be versatile synthetic intermediates. Particularly, Pd(0)[2] or Lewis acid[3] promoted allylic substitution of allylic nitro compounds by nucleophiles has been the subject of considerable recent development. Very recently, during the course of our study directed toward their utilization for organic synthesis, we found that cyclic α-(nitroalkyl)enones underwent replacement of nitro group by stabilized carbon nucleophiles and nitrogen and sulfur ones to give S_N2 type products without the aid of metal catalysts[4]. As an extension of this work, here we report our new findings in that the base-sensitive cyclic α-(nitroalkyl)enones **1**, **2** and **3** react with organocuprates in the presence of TMSCl to afford mono β-conjugate addition products **4** as the corresponding silyl enol ethers which can be utilized for further synthetic transformation (eq 1).

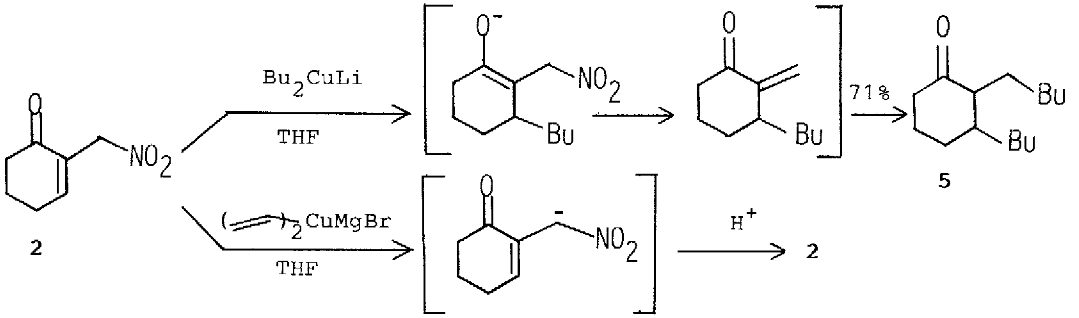


(1)

1, n=1, R^1=H; **2**, n=2, R^1=H;
3, n=2, $R^1=CH_2CH_2COCH_3$

4

Initially we predicted that α-(nitroalkyl)enones were not appropriate substrates toward 1,4-conjugate addition of organocopper reagents because of the existence of quite acidic α-nitro protons[5], and that even though the conjugate addition occurred it would be difficult to obtain mono β-adduct selectively due to the ease of β,β'-double conjugate addition as observed in the reaction of analogous enones bearing the β'-heteroatom substituent with organocuprates[6]. In fact, subjection of 2-(nitromethyl)cyclohexenone (2) to Bu_2CuLi and $(vinyl)_2CuMgBr$ in THF at low temperature resulted in the formation of β,β'-dibutylated product 5 (71% yield) and quantitative recovery of 2, respectively (eq 2 and 3).



(2)

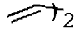
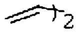
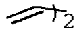
(3)

In order to overcome both problems which we encountered, we sought reaction conditions which allow 1,4-conjugate addition to prevail over abstraction of the acidic proton from nitroalkyl group by R_2CuM complexes and facilitate trapping of the intermediate enolates resulting from initial conjugate addition. Addition of TMSCl to the reaction mixture is promising, since it has been extensively recognized that TMSCl serves to enhance the rate of addition of cuprates to enones[7] and its use leads directly to silyl enol ethers[8]. Indeed TMSCl turned out to be indispensable for successful conjugate addition of cuprates to α-(nitroalkyl)enones (eq 1). Results are summarized in Table I.

To optimize the reaction conditions, **2** was subjected to various organocopper reagents[9]. The present addition reaction to α-(nitromethyl)enones was highly dependent on the type of organocopper reagents employed. With respect to transfer of alkyl and phenyl groups, the use of more than one equivalent of homocuprates Bu_2CuM, Me_2CuM and Ph_2CuM (M=Li or MgX) led to the best results (runs 1,8 and 9). Two equiv of heterocuprate BuCu(CN)Li was also effective, albeit the reduced yield, whereas PhCu(CN)Li failed to give the conjugate adduct; large amount of **2** was recovered (runs 4,5 and 10). Both 0.6 equiv of Bu_2CuLi and 1.1 equiv of BuCu failed to bring the reaction to completion despite the presence of HMPA as additive and prolonged reaction time, resulting in around 50% reaction conversion (runs 2 and 6)[7d]. Copper-catalyzed conjugate addition of BuMgBr in the presence of TMSCl and HMPA was infeasible (run 7)[7c]. On the whole, no pronounced effect of HMPA on the yield enhancement was noted. Chemoselective conjugate addition occurred regardless of the presence of another keto group in the same molecule (run 19). 2-(Nitromethyl)-cyclopentenone (**1**) underwent a similar conjugate addition (runs 16,17 and 18).

Aspect of transfer of vinyl group was quite different from that of alkyl and phenyl groups. To induce the transfer of vinyl group in $(vinyl)_2CuMgBr$ large excess amount of TMSCl was necessary, but only β,β'-divinylated product was obtained along with recovered **2** (runs 11 and 12). $(Vinyl)_2CuMgBr \cdot BF_3$ also effected β,β'-double conjugate addition (run 13). These results imply that the high basicity and nucleophilicity of $(vinyl)_2CuMgBr$ complex or its equilibrating counterpart vinylMgBr might cause abstraction of the acidic α-nitro proton and nucleophilic desilylation of once formed silyl enol ether, eventually leading to the recovery of α-(nitromethyl)enones and the double conjugate addition products, respectively, as shown in eq 2 and 3.

Table I. TMSCl promoted conjugate addition to α-(nitroalkyl)enones (eq 1).

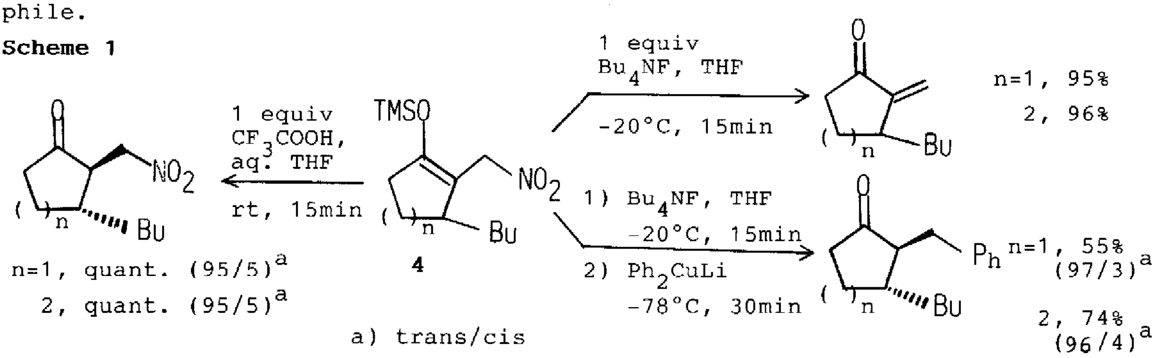
run	nitroenone	copper reagent (equiv)	TMSCl (equiv)	temp (°C)	time	yield(%) **4**[a]	yield(%) **2**[b]
1	**2** (n=2,R^1=H)	Bu_2CuLi (1.1)	2.0	-78	10 min	98	0
2	**2**	Bu_2CuLi (0.6)[c]	2.0	-78	3 h	45	45
3	**2**	$Bu_2CuMgCl$ (2.0)	2.0	-78	2 h	95	0
4	**2**	BuCu(CN)Li (1.1)	2.0	-78	10 min	12	48
5	**2**	BuCu(CN)Li (2.0)	2.0	-78	10 min	85	0
6	**2**	BuCu (1.1)[c]	2.0	-78	3 h	42	53
7	**2**	BuMgCl (2.0)[c] (10% CuBr·Me_2S)	2.0	-78	3 h	0	91
8	**2**	Me_2CuLi (1.1)	2.0	-78	10 min	90	0
9	**2**	Ph_2CuLi (1.1)	2.0	-78	10 min	80[d]	0
10	**2**	PhCu(CN)Li (2.0)	2.0	-78	10 min	0	84
11	**2**	( $)_2$CuMgBr (2.0)[c]	2.0	-78 then -50	10 min 10 min	0	65
12	**2**	( $)_2$CuMgBr (2.0)	20.0	-78	30 min	0[e]	15
13	**2**	( $)_2$CuMgBr·BF_3 (2.0)	2.0	-78 then -50	10 min 10 min	0[f]	0
14	**2**	 Cu(CN)MgBr (2.0)	2.0	-78 then -50	10 min 10 min	0[g]	62
15	**2**	 Cu(CN)MgBr·BF_3 (2.0)	2.0	-78 then -50	10 min 10 min	51[h]	30
16	**1** (n=1,R^1=H)	Bu_2CuLi (1.1)	4.0	-78	10 min	74	
17	**1**	Me_2CuLi (1.1)	4.0	-78	10 min	78	
18	**1**	Ph_2CuLi (1.1)	4.0	-78	10 min	51[d]	
19	**3** (n=2,R^1=CH_2CH_2COMe)	Bu_2CuLi (1.1)	2.0	-78	10 min	96	

a) Yields refer to isolated yields of the silyl enol ethers. b) Recovery. c) HMPA (2 equiv) was added. d) Isolated as a ketone upon treatment with CF_3COOH in aqueous THF. e)f)g) β,β'-Divinylated product was obtained in 83%(e), 67%(f) and 35%(g) yield. h) Isolated as a ketone.

Accordingly, the use of (vinyl)Cu(CN)MgBr·BF_3, a combination of Lewis acid and less nucleophilic heterovinylcuprate, could prevent the double conjugate addition to a great extent and afford β-monovinylated product as a desilylated form (run 15)[10].

To probe the synthetic utility of silyl enol ethers **4** obtained, transformation of **4** into an important class of compounds was performed. Typical examples are illustrated in Scheme 1. Hydrolysis with CF_3COOH in aqueous THF produced 2-(nitromethyl)cycloalkanones quantitatively, a class of compounds not generally available by standard synthetic methods. Treatment of **4** with Bu$_4$NF led to α-exo-methylene ketones in excellent yield, which in turn gave 2,3-disubstituted cycloalkanones upon 1,4-conjugate addition of a second nucleophile.

Scheme 1



a) trans/cis

References and Notes

1) For the general synthetic methods, see: (a) Tamura, R.; Sato, M.; Oda, D. J. Org. Chem. **1986**, 51, 4368. (b) Tamura, R.; Kato, M.; Saegusa, K.; Oda, D.; Egawa, T.; Yamamoto, T. J. Org. Chem. **1987**, 52, 1640. (c) Ono, N.; Hamamoto, I.; Kamimura, A.; Kaji, A.; Tamura, R. Synthesis **1987**, 258.

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9) CuBr·SMe$_2$ and CuCN were employed for the preparation of organocopper reagents in the present work. For a study on Cu(I) salts, see: Bertz, S.H.; Gibson, C.P.; Dabbagh, G. Tetrahedron Lett. **1987**, 28, 4251.
General experimental procedure: To the organocopper reagents (1.8 to 6.0 mmol) in THF (5 mL) was added dropwise a mixture of the nitroenone (3.0 mmol) and TMSCl (6.0 to 12 mmol) in THF (3 mL) at -78°C. After stirring for the stated period of time, water (30 mL) was added. The aqueous mixture was extracted with ether. The ether extracts were washed with water, dried over MgSO$_4$, and concentrated to give the TMS enol ether in a high state of purity.

10) For the transfer of vinyl group, α-(dialkylaminomethyl)enone has been reported to be an appropriate substrate for mono β-conjugate addtion to give α-exo-methylene ketone, see: Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. J. Org. Chem. **1988**, 53, 5590.

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