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ALDOL REACTION OF ALLENOLATES GENERATED VIA 1,4-ADDITION OF IODIDE ANION OR ITS EQUIVALENT TO α,β-ACETYLENIC KETONES

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Abstract: TMSI, Et_2AlI and $(n\text{-}Bu)_4NI/TiCl_4$ smoothly added to α,β-acetylenic ketones in a 1,4-fashion to yield allenolates 2, which reacted with aldehydes providing aldol adducts in good overall yield. A high Z-stereoselectivity was achieved by use of $(n\text{-}Bu)_4NI/TiCl_4$ at -78°C, while a high E-stereoselectivity occurred at 0°C.

Conjugate addition of cuprates to α,β-unsaturated carbonyl compounds, followed by trapping the resultant enolates with various electrophiles, has been demonstrated as a powerful solution to various synthetic problems.[1] In the preceding papers,[2] we reported a facile synthesis of β-iodovinyl ketones via acetylenic ketones. In the course of this study, we observed the formation of a self-condensation product such as 3 when 1-octyn-3-one (1) was treated with Et_2AlI or $(n\text{-}Bu)_4NI/TiCl_4$ in CH_2Cl_2. This result suggested that the intermediate 2 might be useful to achieve a tandem conjugate addition-aldol reaction of α,β-acetylenic ketones.[3] In this communication, we would like to report the reaction of α,β-acetylenic ketones with iodide anion or its equivalent, followed by an aldol process, to yield α-substituted-β-iodovinyl ketones.[4]

Scheme 1

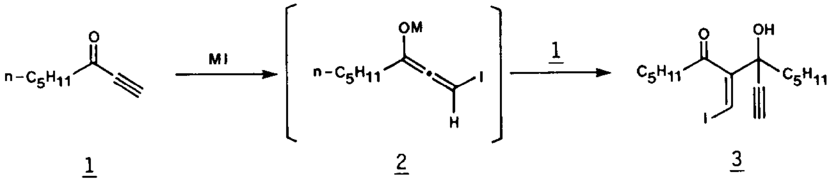
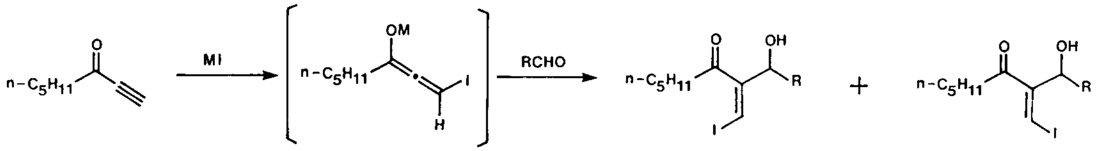


TABLE 1

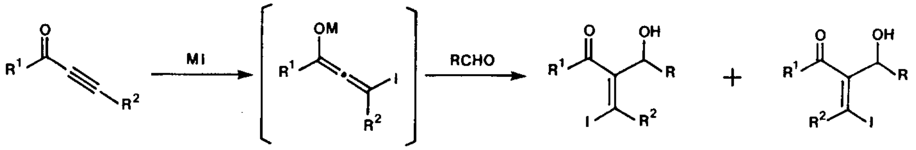


1a 2a Z-4a E-4a

Run	MI/CH_2Cl_2	RCHO	Conditions	Z-4a (%)	E-4a (%)
1	TMSI/$TiCl_4$	PhCHO	-78°C, 1 hr	38[a]	17[a]
2	TMSI/$(n\text{-}Bu)_4NF$	PhCHO	RT, 3.5 hr	39[a,b]	17[a,b]
3	TMSI/TMSOTf	$PhCH(OMe)_2$	-78°→-10°C, 2 hr	81 (Z:E = 2.5:1)	
4	Et_2AlI	PhCHO	-78°C, 1 hr	64	16
5	Et_2AlI	PhCHO	0°C, 30 min	--	63
6	Et_2AlI	CH_3CHO	-78°C, 20 min	54	22
7	Et_2AlI	CH_3CHO	-78°C, 1 hr + RT, 1.5 hr	--	46
8	Et_2AlI	i-PrCHO	-78°C, 5 min	45	[c]
9	$(n\text{-}Bu)_4NI/TiCl_4$	PhCHO	-78°C, 10 min	80	2
10	$(n\text{-}Bu)_4NI/TiCl_4$	PhCHO	0°C, 20 min	2	78[d]
11	$(n\text{-}Bu)_4NI/TiCl_4$	CH_3CHO	-78°C, 10 min	71	8
12	$(n\text{-}Bu)_4NI/BF_3 \cdot Et_2O$	PhCHO	-78°C, 20 min	42	18
13	TiI_4	PhCHO	0°C, 1.5 hr	--	45

[a] E-1-Iodo-1-octen-3-one was also isolated in about 30% yield.
[b] After hydrolysis of the TMS derivative with citric acid.
[c] E-4, contaminated with an unidentified product, was obtained in about 10% yield.
[d] The product contained a fair amount of the chloro derivative (I:Cl=3:1).

TABLE 2



1 2 Z-4 E-4

	Substrates		Reagents/Solvent	Conditions	RCHO	Z-4 (%)	E-4 (%)
	R^1	R^2					
1b:	i-Pr	H	$(n\text{-}Bu)_4NI/TiCl_4/CH_2Cl_2$	-78°C, 15 min	Ph	79[a]	1
1c:	Ph	H	$(n\text{-}Bu)_4NI/TiCl_4/CH_2Cl_2$	-78°C, 10 min	Ph	82	1.5
1d:	OMe	H	$(n\text{-}Bu)_4NI/TiCl_4/CH_2Cl_2$	-78°C, 1.5 hr	Ph	53	4
			$(n\text{-}Bu)_4NI/TiCl_4/CH_2Cl_2$	0°C, 40 min	Ph	52	5
1e:	n-Pen	n-Bu	$(n\text{-}Bu)_4NI/TiCl_4/CH_2Cl_2$	-78°C, 30 min	Ph	48[b]	25

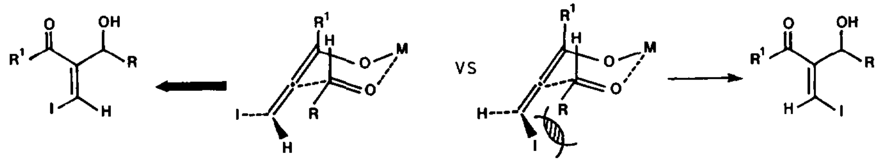
[a] mp 106-107°C. [b] mp 47-49°C.

As demonstrated in the preceding papers,[2] TMS-allenolates[5] are readily available by reacting acetylenic ketones with trimethylsilyl iodide (TMSI). We first examined its reactivity toward aldehydes (Table 1). The TMS-allenolate 2a (M=TMS), prepared in situ by treatment of 1a with TMSI (1 eq) in CH_2Cl_2 at -78°C, was reacted with benzaldehyde (1 eq) and $TiCl_4$ (1 eq)[3,6] at -78°C, to yield Z-4a (38% yield) and E-4a (17% yield) (run 1).[7,8] Fluoride anion[3,9] instead of $TiCl_4$ did not improve the efficiency of the aldol process (run 2) but a catalytic amount of TMSOTf[3,10] showed a dramatic improvement (run 3).

We next focused our attention on the use of other iodide reagents. When 1a was treated with Et_2AlI[11] in the presence of aldehydes in CH_2Cl_2, Z-4 (R=Ph or Me) was obtained as the major product at -78°C (run 4, 6), whereas E-4 (R=Ph or Me) was obtained exclusively at 0°C or -78°C -> room temperature (run 5, 7). These results indicate that Z-4 is a kinetically controlled product, while E-4 is a thermodynamically controlled product. $(n\text{-}Bu)_4NI/TiCl_4$ conditions provided even better selectivity as shown in run 9-11, although halogen exchange occurred to some extent at 0°C (run 10).[12] To prevent the formation of chloro derivatives TiI_4 was tested albeit with moderate success (run 13).

The high Z selectivity under kinetically controlled conditions could be explained by the analogy of the stereoselective aldol reaction of enolates via a cyclic transition state as illustrated in Figure 1.[3] A serious non-bonded interaction between I and R is obvious in the transition state B.

Figure 1



Z-4a A B E-4a

We have briefly examined the generality of this method by its application to other types of acetylenic ketones and an ester. The results are summarized in Table 2, which reveal some interesting potentials of the current coupling reaction. It is noteworthy to add that this aldol coupling reaction is applicable to ketones as well.[13]

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References and Notes

1. There are numerous examples known in the literature. For example, see G. Stork and J. d'Angelo, J. Am. Chem. Soc., 96, 7114 (1974). For more recent examples, see T. Tanaka,

N. Okumura, K. Bannai, A. Hazato, S. Sugiura, K. Manabe, and S. Kurozumi, Tetrahedron Lett., 26, 5575 (1985) and references cited therein.

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6. For $TiCl_4$-induced aldol reactions, see (a) T. Mukaiyama, K. Banno, and K. Narasaka, J. Am. Chem. Soc., 96, 7503 (1974), (b) K. Saigo, M. Osaki, and T. Mukaiyama, Chem. Lett., 989 (1975), and (c) T. H. Chan, T. Aida, P. W. K. Lau, V. Gorys, and D. N. Harpp, Tetrahedron Lett., 4029 (1979).
7. Satisfactory spectroscopic data (^{1}H-NMR, IR, MS) were obtained for all the compounds in this paper. The compounds 3, Z-4a,b,d,g, and E-4a,b gave satisfactory elemental analyses (C, H).
8. The E- and Z-stereochemical assignment was based on ^{1}H-NMR spectra. Due to the deshielding effect of the carbonyl group, the β-H of the enone group in the E-isomer appeared at more than 1 ppm lower field than that in the corresponding Z-isomer; for example, Z-4a: 6.55 ppm vs. E-4a: 7.96 ppm; Z-4b: 6.59 ppm vs E-4b: 7.75 ppm; and Z-4c: 6.51 ppm vs E-4c: 7.88 ppm.
9. For tetraalkylammonium fluoride-induced aldol reactions, see (a) E. Nakamura, M. Shimizu, and I. Kuwajima, Tetrahedron Lett., 1699 (1976), (b) R. Noyori, K. Yokoyama, J. Sakata, I. Kuwajima, E. Nakamura, and M. Shimizu, J. Am. Chem. Soc., 99, 1265 (1977), (c) W. A. Kleschick, C. T. Buse, and C. H. Heathcock, J. Am. Chem. Soc., 99, 247 (1977), and (d) C. H. Heathcock, C. T. Buse, W. A. Kleschick, M. C. Pirrung, J. E. Sohn, and J. Lampe, J. Org. Chem., 45, 1066 (1980).
10. For TMSOTf-induced aldol reactions, see S. Murata, M. Suzuki, and R. Noyori, J. Am. Chem. Soc., 102, 3248 (1980).
11. For aldol reactions of aluminium enolates resulting from 1,4-addition of Me_2AlSPh to α,β-unsaturated carbonyl compounds, see reference 4d.
12. A typical experimental procedure is illustrated by the reaction of 1-octyn-3-one (1a) with $(n\text{-}Bu)_4NI/TiCl_4$ and benzaldehyde. To a mixture of 1-octyn-3-one (302 mg, 2.4 mmol), $(n\text{-}Bu)_4NI$ (0.90 g, 2.4 mmol) and benzaldehyde (0.28 g, 2.7 mmol) in CH_2Cl_2 (10 ml) was added titanium tetrachloride (0.30 ml, 2.7 mmol) slowly at -78°C. After stirring for 10 min at -78°C, the reaction mixture was diluted with CH_2Cl_2, washed with water, sat. $NaHCO_3$, and brine, and dried over $MgSO_4$. After filtration the organic layer was evaporated under reduced pressure to give a residue, which was separated by silica gel column chromatography (n-Hex/AcOEt) to give Z-4a (mp 32-34°, 699 mg, 80%) and a 1:2 mixture (45 mg) of E-4a and 3 (2% and 3%, respectively).
13. M. Taniguchi, unpublished results.

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