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SYNTHESES WITH DIHYDRO-1,3-OXAZINES. IX.

A SIMPLE SYNTHESIS OF α-PHENYLALDEHYDES AND KETONES

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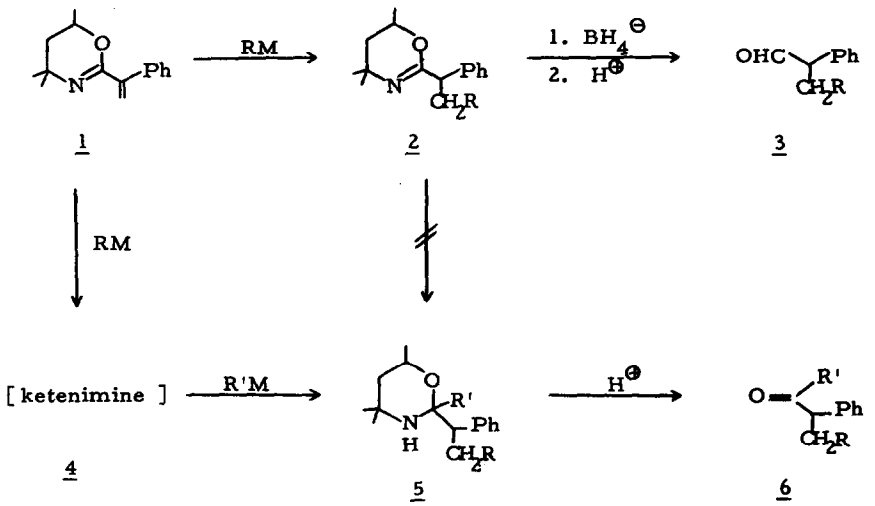
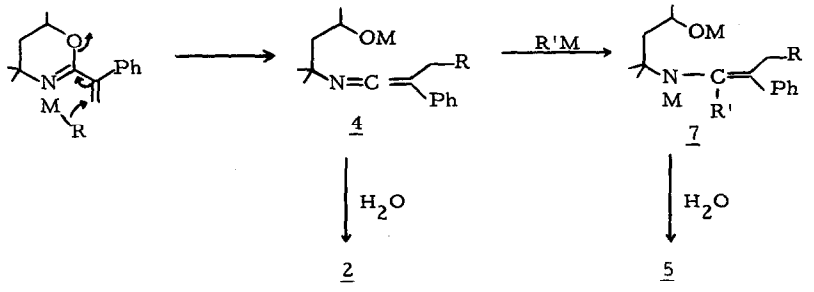
We wish to report a facile approach to aliphatic aldehydes 3 and ketones 6 containing an α-phenyl substituent which originates from the readily available α-styryldihydro-1,3-oxazine (1).[1] This technique represents a further extension of our earlier efforts utilizing dihydro-1,3-oxazines as useful precursors to aldehydes,[2] ketones,[3] and carboxylic acids.[4]



1 2 3

4 5 6

The addition of 2.5 equiv of n-butylmagnesium bromide to 1 in THF at all temperatures between -78° and 25° affords the dialkylated tetrahydro-1,3-oxazine 5 (R=R'=n-Bu) in 73% yield, which in its crude form, was directly cleaved (aqueous oxalic acid, reflux, 2 hr) to the ketone 6 (R=R'=n-Bu) in 68% overall yield (Table 1). The use of the bulky reagent, cyclohexylmagnesium bromide (2.5 equiv), gave after reaction with 1, a 98% yield of the monoalkylated oxazine 2 (R=cyclohexyl). However, 2 could be smoothly reduced to the tetrahydro-1,3-oxazine 5 (97%, R'=H, R=cyclohexyl) by treatment with sodium borohydride (-35°, EtOH-THF-H_2O) and readily cleaved to α-cyclohexylmethyl phenylacetaldehyde 3 (R=cyclohexyl) in excellent overall yield (entry 8, Table 1).[2] The fact that a second equiv of cyclohexyl Grignard would not add to give 5, did not deter the immediate use of a smaller organometallic (MeLi or EtMgBr) in the second step. In this manner, good yields of the dialkylated adduct were obtained (entry 2, Table 1). This behavior was also noted with other bulky organometallics (i-PrLi, s-BuLi, t-BuLi) which added only to give the monoalkylated products yet allowed the introduction of a primary alkyl metallic leading to the ketone precursors 5 (entries 1, 5, 6). The addition of phenylmagnesium bromide as the second reagent (5, R'=Ph, R=t-Bu) appears to be the limiting case with respect to steric approach (entry 4).

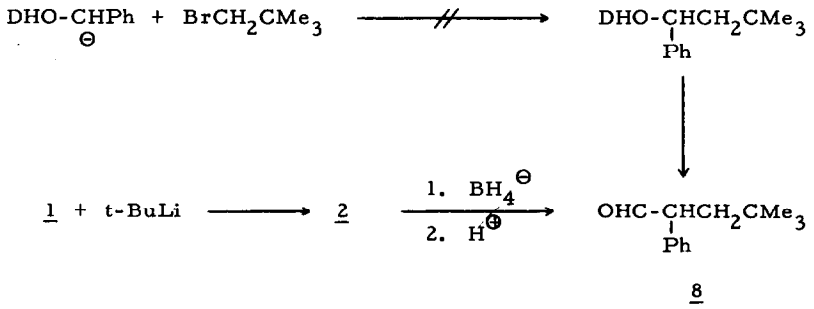


The mechanism of addition to 1 was found to involve the ketenimine intermediate 4 which was isolated by concentration of the THF solution after addition of 1.0 equiv of t-butyllithium to 1. The residue (hygroscopic salt) revealed an intense band at 2010 cm^{-1} (Nujol) characteristic of the ketenimine[5] and is thus related to the α-methylketone synthesis from 2-isopropenyldihydro-1,3-oxazine.[3] Addition of water to the THF solution of the kete-

nimine 4 results in rapid recyclization to the monoalkylated oxazine 2 whereas, addition of a second organometallic reagent leads to alkylation (7). The latter upon addition of water is converted to the enamine 7 (M=H) which is the open chain tautomer of the tetrahydro-1,3-oxazine 5.

The only serious limitation in this ketone synthesis is found when two different primary alkylmetallics (e.g. n-BuLi followed by n-PrLi) are employed. The resulting ketone will contain a uniform R-substituent but R' will be a mixture of both reagents (6 R=n-Bu, R'=n-Bu + n-Pr). However, cautious stoichiometric addition (1.0 equiv of each reagent) can minimize the mixture such that the desired mixed ketone (R=n-Bu, R'=n-Pr) may be efficiently obtained. This mixed addition cannot be carried out using Grignard reagents since no alkylation (to 2) occurs unless there are at least 2.0 equiv of RMgX added.

Among the major advantages of this method is the formation of neopentyl aldehydes 8 which would not form from the carbanion of 2-benzyldihydro-1,3-oxazine (DHO-CH_2Ph) due to the well known inertness of neopentyl halides toward nucleophilic substitution.



It is noteworthy that this process provides an alternative to Brown's [6] synthesis of aldehydes and ketones (organoborane-CO method) when the required olefins are inaccesible. [7]

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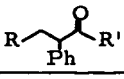
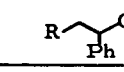
TABLE 1

α-Phenylketones

entry	RM (equiv)	R'M (equiv)	% 5	 (6)[a,b]	2,4-DNP
1.	t-BuLi (1.2)	MeLi (1.2)	93	84	120-122°
2.	$C_6H_{11}MgBr$ (2.5)	MeLi (1.2)	98	79	126-127°
3.	n-BuMgBr (2.5)	n-BuMgBr	73	68	-
4.	t-BuLi (1.2)	PhMgBr (2.0)	25	13	-
5.	s-BuLi (1.2)	MeLi (1.2)	96	83	84-86°
6.	i-PrLi (1.2)	EtMgBr (1.3)	96	73	93-95°

α-Phenyl Aldehydes

entry	RM (equiv)	% 2	% 5 (R'=H)	 (3)[a,b]	2,4-DNP
7.	t-BuLi (1.2)	95	97	71	172-173°
8.	$C_6H_{11}MgBr$ (2.5)	99	98	94	155-157°

a) All carbonyl compounds were previously unreported and gave satisfactory elemental, mass, and spectral analyses. b) Overall yields based upon 1; reactions were performed on 25-50 mmole scale and yields represent isolated material.

REFERENCES

1. Prepared from 2-benzyl-4,4,6-trimethyldihydro-1,3-oxazine (Columbia Organic Chem., Columbia, S.C.) by azeotropic condensation (24 hr) with 1.5 equiv paraformaldehyde in toluene containing a trace of trifluoroacetic acid; bp 93-95 (0.2 mm); ir 1610, 1640 cm^{-1}.

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3. A.I. Meyers and A.C. Kovelesky, J. Am. Chem. Soc., 91, 0000 (1969).

4. A.I. Meyers, I.R. Politzer, B.K. Bandlish, and G.R. Malone, ibid., 91, 0000 (1969).

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6. H.C. Brown, Accounts Chem. Res., 2, 65 (1969).

7. Experimental details will be sent to anyone requesting them.