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A simple, user-friendly process for the homologation of aldehydes using tosylhydrazone salts

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Abstract

Aldehydes can be homologated to ketones in moderate to good yields using aryldiazomethanes generated in situ from tosylhydrazones. Chiral aldehydes can be employed with almost complete retention of configuration. The tosylhydrazones can also be generated in situ from the corresponding aldehyde leading to a one-pot process for coupling two different carbonyl compounds to give ketones.

Homologation of aldehydes and ketones by carbon insertion methods is a valuable tool in organic synthesis.[1–6] Most methods employ diazoalkanes,[2–6] but these processes are limited due to competing reactions such as multiple homologation, and oxirane formation. The extent of such competing processes has been limited using hindered aluminium-based Lewis acids.[5] A further practical limitation of this methodology is the need to synthesise and handle diazocompounds, which, since they are invariably toxic and unstable, precludes their use on a large scale. As an alternative to the use of diazoalkanes, Katritzky[1a,b] has reported the use of 1-(arylmethyl)-benzotriazoles for homologation of carbonyl compounds which works effectively because the benzotriazole moiety is both an anion stabilising group and leaving group. However, high temperatures are required in this process (65–210°C). We have recently reported a new method for the epoxidation of carbonyl compounds using catalytic amounts of sulfides and diazocompounds.[7] Cognisant of the practical limitations surrounding the use and handling of diazocompounds we sought and developed a method for generating such reactive intermediates in situ and successfully applied this method to catalytic asymmetric epoxidation,[8] aziridination[8] and cyclopropanation[8] (Scheme 1). We also considered the potential application of this new

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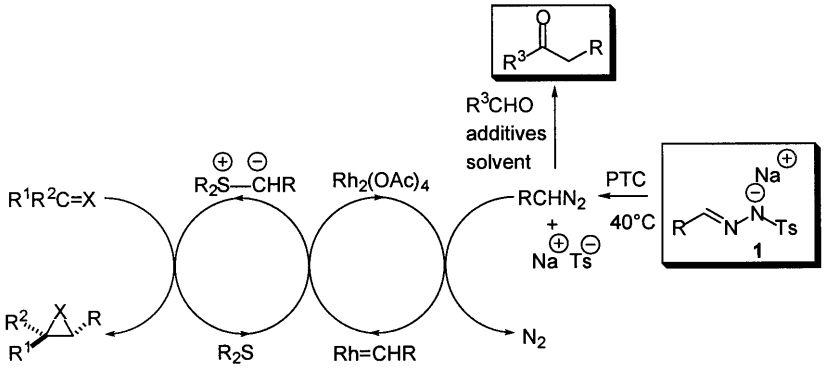


Scheme 1. In situ generation of diazocompound and applications to epoxidation (X = O), aziridination (X = NTs) and cyclopropanation ($X = CH_2$) and proposed application to homologation of carbonyl compounds

protocol for generating diazocompounds towards a user-friendly method for homologation of carbonyl compounds and in this paper report our success in achieving this objective.

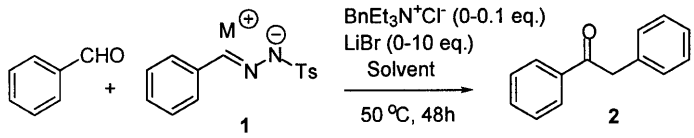
Aryldiazomethanes have been employed in the homologation of aldehydes using an iron-based Lewis acid[4a] and LiBr in Et_2O.[4b] We therefore began our studies using our in situ method for generating $PhCHN_2$ and tested the reaction in a several ethereal solvents in the presence of an excess of LiBr (ether was reported to be best).

Only moderate yields of the homologated ketone were obtained even though the hydrazone had been completely consumed (Table 1, entries 1–3). THF appeared to be the optimum solvent and so further studies were conducted in this solvent. We decided to confirm that all the additives were required (entries 4, 5), but were surprised to find that the *homologation reaction actually performed better in the absence of both LiBr and the PTC*. Thus, only the reagents required in the coupling were necessary for the reaction. We subsequently investigated the effect of solvent on the yield of the reaction (entries 6–11) and found that THF and THF/H_2O gave the highest yields. These solvents were therefore selected for further optimisation. As it was found that significant amounts of the aldehyde remained we decided to increase the quantity of the tosylhydrazone salt and also tested the Li salt as well (entries 12–17). Improved yields were indeed obtained with increased loadings of the tosylhydrazone salt but the yields plateaued at 1.5 equivalents. No improvements were obtained using the lithium derivative and so the optimum conditions were as shown in entry 15. We also determined that 10% water in THF was optimum (entries 18 and 19).

During the course of the reactions a steady state concentration of the diazocompound is formed as shown by the gradual change in colour of the reaction mixture from colourless to pink and finally back to colourless at the end. Phenyldiazomethane is a deep red liquid.

Careful analysis of the reactions conducted in THF and in THF/H_2O revealed significant differences in the efficiency and selectivity of the reaction (Scheme 2). In THF reactions were less efficient (a substantial amount of aldehyde remained), but only the product of H-migration **2** was observed. In contrast, in THF/H_2O, reactions were considerably more efficient (no aldehyde remained), but phenyl migration competed with H-migration and the aldehyde that formed was further homologated to give **3**. In homologation of aldehydes with diazocompounds, the main product results from H-migration, but a protic solvent promotes aryl[6] and alkyl[5a] migrations (as observed). Thus, for cleaner reactions aprotic solvents should be employed but higher yields can be achieved in the presence of proton donors.

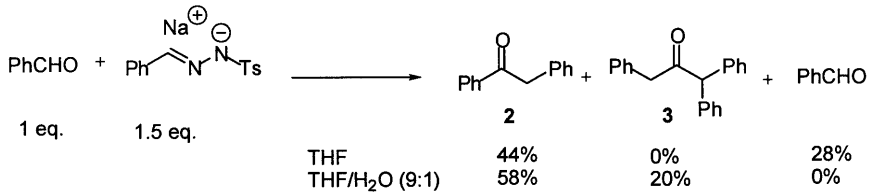
Table 1
Optimisation of reaction[a]



Entry	Salt **1** (equiv.)	Solvent	PTC (equiv.)	LiBr (equiv.)	Yield (%)[b]
1	1	Et_2O	0.1	10	6
2	1	1,4-Dioxane	0.1	10	29
3	1	THF	0.1	10	38
4	1	THF	0	10	36
5	1	THF	0	0	52
6	1	1,4-Dioxane	0	0	9
7	1	MeCN	0	0	47
8	1	DMSO	0	0	11
9	1	DMF	0	0	11
10	1	MeOH	0	0	42
11	1	THF/H_2O (9:1)	0	0	50
12	1.5	THF	0	0	49
13	2.0	THF	0	0	49
14	1.5-Li	THF	0	0	42
15	**1.5**	**THF/H_2O (9:1)**	**0**	**0**	**59**
16	2.0	THF/H_2O (9:1)	0	0	59
17	1.5-Li	THF/H_2O (9:1)	0	0	54
18	1.5	THF/H_2O (19:1)	0	0	51
19	1.5	THF/H_2O (4:1)	0	0	27

[a] Experimental procedure: to a suspension of Na/Li-**1** in the solvent chosen was added PhCHO under nitrogen at rt. The mixture was stirred at 50°C until all the hydrazone was consumed (followed by TLC) and disappearance of the red colour of the phenyldiazomethane (normally occurred after 48 h). After work up the resulting oil was analysed by GC and ^{1}H NMR.

[b] Yields calculated by GC using dibenzyl ether as internal standard.

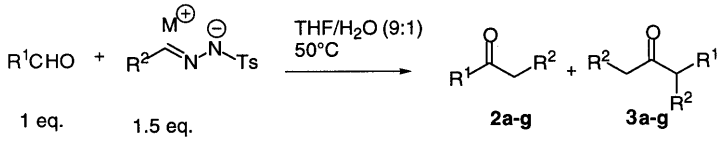


Scheme 2. Effect of water on the reaction

The optimum conditions were tested with a range of aldehydes and several different tosylhydrazone salts (Table 2). In most cases good yields of the homologated products derived from H-migration were obtained together with variable but much smaller amounts of products derived from R^1 migration.

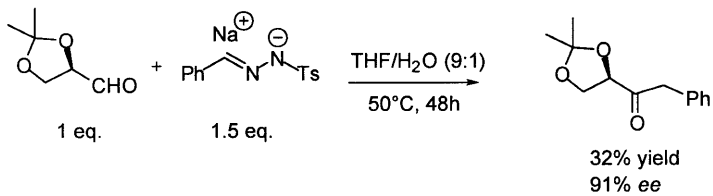
The process is further illustrated by the homologation of glyceraldehyde acetonide (Scheme 3). Although the homologated product was only obtained in moderate yield it was formed with high enantiomeric excess[9] and obtained directly and simply.

Table 2
Homologation of a range of aldehydes with various tosylhydrazone salts[a]



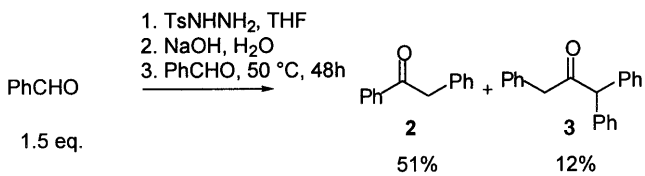
R^1	R^2	Yield **2a–j**[b]	Yield **3a–j**[b]
p-MeC_6H_4	Ph	52	20
o-MeC_6H_4	Ph	48	15
p-$MeOC_6H_4$	Ph	38 (45% ald)	17
p-$NO_2C_6H_4$	Ph	78	21
p-ClC_6H_4	Ph	39	22
2-Furyl	Ph	58	0
n-C_7H_{15}	Ph	46	32
c-C_6H_{11}	Ph	62	21
Ph	*p*-ClC_6H_4	41	13
Ph	*o*-MeC_6H_4	33	12

[a] Experimental procedure: to a suspension of **1** (1.5 mmol) in THF/H_2O 9:1 (3.3 mL) was added aldehyde (1 mmol) under nitrogen at rt. The mixture was stirred at 50°C until all the hydrazone was consumed (followed by TLC) and disappearance of the red colour of the phenyldiazomethane (normally 48 h).
[b] Isolated yields.



Scheme 3. Homologation using a chiral aldehyde

Finally, we have discovered that the process can be simplified further by generating the tosylhydrazone salt in situ from the corresponding aldehyde using very simple reagents without significantly compromising the yield of the homologated ketone (Scheme 4). Thus, two different aldehydes can be coupled together in one pot to give ketones.



Scheme 4. One pot homologation process

Note added in proof: Related work on aldehyde homologations using tosyl hydrazone salts has recently appeared: Angle, S. R.; Neitzel, M. L. *J. Org. Chem.* **2000**, *65*, 6458–6461.

Acknowledgements

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9. Enantiomeric excess was determined by HPLC using a Chiracel® OD column; mobile phase: 21% *i*PrOH, 79% hexane; flow rate (mL/min): 1; first enantiomer: 21.2 min. and second enantiomer 22.3 min (*R* enantiomer).