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Addition of carbon nucleophiles to aldehyde tosylhydrazones of aromatic and heteroaromatic-compounds: total synthesis of piperine and its analogs[†,‡]

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Abstract

Addition of carbon nucleophiles to aldehyde tosylhydrazones of aromatic and heteroaromatic compounds is reported. New observations have been made wherein alkylative reduction is observed in some cases whereas alkylative fragmentation is noticed in others. These findings are exploited in the synthesis of the useful alkaloid piperine and its analogs. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: toluene-*p*-sulphonylhydrazine; piperine; anti-feedant; insecticide.

Tosylhydrazones of carbonyl compounds are gaining importance not only as a tool for purification of unstable aldehydes but also because of their ability to undergo novel nucleophilic additions and fragmentations.[1,2] Our group was the first to discover a new application of aldehyde tosylhydrazones wherein sugar hydrazones[3] and epoxy hydrazones[4] undergo alkylative fragmentation to generate chiral allyl alcohols.[5] These chiral allyl alcohols were efficiently utilized by Schmidt et al. for the total synthesis of sphingosines.[6] More recently the Myers group has reported[7] the reductive coupling of carbon nucleophiles to sugar hydrazones. Inspired by all of these reports we have undertaken a programme to study the reactions between carbon nucleophiles (RMgX and RLi) on aldehyde tosylhydrazones of aromatic and heteroaromatic scaffolds. New findings pertaining to this study are presented herein.

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‡ Dedicated to Dr. A. V. Rama Rao on his 65th birthday.

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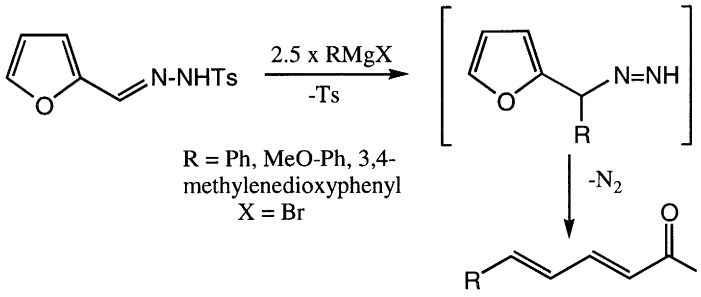


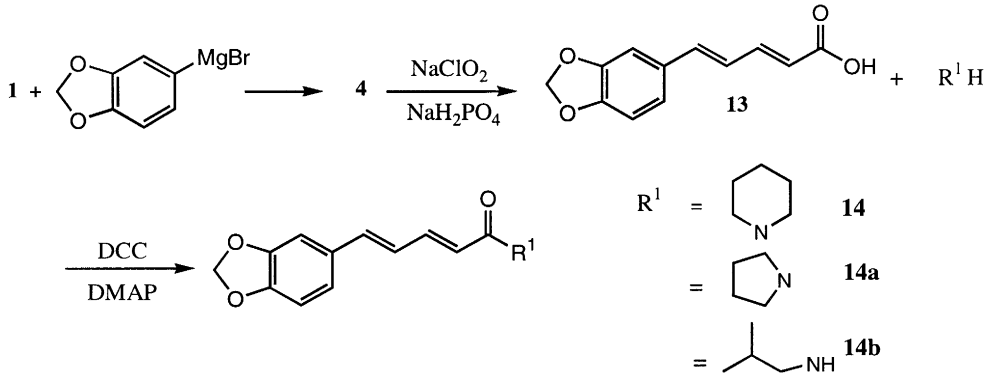
(1)

Readily available furfural was derivatized as its hydrazone (toluene-*p*-sulphonylhydrazine CH_3OH, rt, 15 h) which was treated with PhMgBr (2.5 equiv.) in anhydrous THF to realize 5-phenyl-2*E*,4*E*-pentadienal **2** in 75% isolated yield.

Accordingly hydrazone **1**, on treatment with nucleophiles such as *p*-methoxyphenylmagnesium bromide and 3,4-methylenedioxyphenylmagnesium bromide, furnished the corresponding dienals **3** and **4** in 70 and 80% yields, respectively.[8,12d] Thus furfuraldehyde has been efficiently utilized as a five-carbon open chain dienal equivalent. Exposure of the furfural hydrazone to aliphatic nucleophiles (substrate 1), however, produced the corresponding alkylated products (**5**, **5a**, **6**) without any traces of ring-opened products. This unusual behavior between aromatic and aliphatic nucleophiles made us believe that both the nucleophilicity and the basicity of the nucleophiles have a direct influence on the outcome of the reaction.[9]

Thiophene 2-carboxyaldehyde toluene-*p*-sulphonylhydrazone **7**, on treatment with an excess of BuLi (5 equiv.), resulted only in the reductive coupling product, 2-pentylthiophene. However, exposure of **7** to phenylmagnesium bromide produced a complex mixture of products, which could not be characterized. Benzaldehyde toluene-*p*-sulphonylhydrazone and naphthaldehyde toluene-*p*-sulphonylhydrazone when treated with BuLi, consistently yielded pentylbenzene and 2-pentylnapthalene in good yields (substrate **9**, **11**).

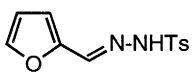
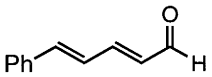
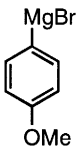
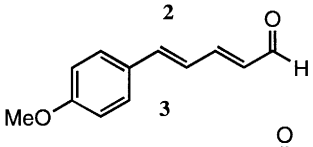
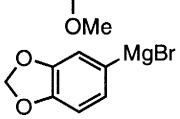
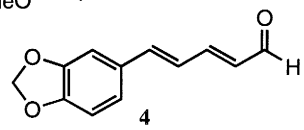
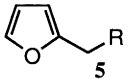
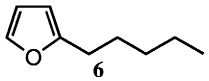
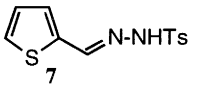
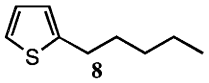
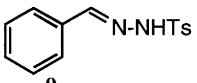
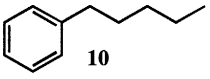
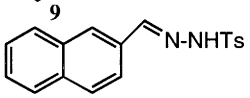
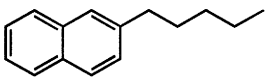
Using this chemistry the dienal **4** was converted to piperine **14**, a bioactive alkaloid (Scheme 1). This alkaloid is found to possess diverse roles in biology especially related to central nervous system disorders, anti-inflammatory, antidepressant, insecticidal and anti-feedant activities.[10] Aldehyde **4** was oxidized to the dienoic acid[11] **13** (75%) on treatment with $NaClO_2$ and NaH_2PO_4 in *t*-BuOH, which was amidated with various amines to produce piperine **14** (72%)[12] and its analogs, **14a** (69%) and **14b** (76%).



Scheme 1.

In conclusion, a highly efficient and novel methodology is developed involving addition of carbon nucleophiles to various aromatic and heteroaromatic aldehyde tosylhydrazones.[13] The products thus

Table 1

Substrate	Reagent	Product	Yield (%) [a]
 **1**	PhMgBr	 **2**	75
1		 **3**	70
1		 **4**	80
1	RMgBr R = *n*-Propyl, *n*-Pentyl	 **5** R = *n*-Propyl **5a** R = *n*-Pentyl	80 75
1	BuLi	 **6**	65
 **7**	BuLi	 **8**	50
 **9**	BuLi	 **10**	70
 **11**	BuLi	 **12**	75

[a] Yields calculated after column chromatography of the products.

formed, both ring cleaved products as well as reductive coupling products, may find widespread application in natural product synthesis.

Acknowledgements

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8. General procedure: preformed alkyl magnesium halide (2.5 mmol) in anhydrous THF (15 mL), was added dropwise to a cold solution of aldehyde toluene-*p*-sulphonylhydrazone (1 mmol) in anhydrous THF (5 mL) under a nitrogen atmosphere. After the reaction mixture was stirred at ambient temperature for 2 h, the reaction mixture was quenched with saturated NH_4Cl solution (10 mL) and extracted with ether (2×25 mL). The combined organic layer was washed with water, brine and dried over Na_2SO_4. The volatiles were removed under vacuum and the residue was purified by column chromatography to afford *trans*-2,4-pentadienal in the yields summarized in Table 1.
9. A free radical mechanism as proposed by Myers (see Ref. 7) may not be ruled out.
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13. Spectral data of compounds: **2**: ^{1}H NMR $CDCl_3$ 200 MHz: δ 9.6 (d, 1H, *J*=6 Hz), 7.62–7.2 (m, 6H), 6.95 (d, 1H, *J*=11.4 Hz), 6.5 (dd, 1H, *J*=12, 18 Hz), 6.25 (dd, 1H, *J*=6, 16 Hz); EI MS: *m/z* 158, 129, 115, 102, 91, 77; **4**: ^{1}H NMR $CDCl_3$ 200 MHz: δ 9.62 (d, 1H, *J*=6.9 Hz), 7.25 (dd, 1H, *J*=9.7, 16.6 Hz), 7.05–6.8 (m, 5H), 6.2 (dd, 1H, *J*=6.2, 16 Hz), 6.05 (s, 2H); EI MS: *m/z* 202, 173, 115, 102, 91, 77; **6**: ^{1}H NMR $CDCl_3$ 200 MHz: δ 7.55 (s, 1H), 7.15 (d, 1H, *J*=4 Hz), 6.5 (m, 1H), 2.8 (t, 2H, *J*=7 Hz), 1.8–1.6 (m, 2H), 1.45–1.2 (m, 4H), 0.9 (t, 3H, *J*=7 Hz); EI MS: *m/z* 123 (M^+-15), 105, 91, 67, 54.