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LETTERS

A General, [1+4] Approach to the Synthesis of 3(5)-Substituted Pyrazoles from Aldehydes.

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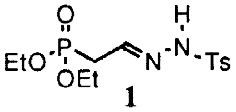
Abstract: A new, one-pot preparation of 3(5)-substituted-1H-pyrazole is described that employs Horner-Emmons reaction of aldehydes with dianion of novel phosphonate **1** and proceeds through cyclization of N-sodium salt of α,β-unsaturated tosylhydrazones **2**. © 1998 Elsevier Science Ltd. All rights reserved.

In the plethora of existing methodologies for the synthesis of pyrazole derivatives, a vast majority relies on the condensation of hydrazine with 1,3-difunctional compounds.[1] The appealing generality of this method is somewhat vitiated by the severe reaction conditions or the multistep sequence usually required to access the starting material. In the case of 3(5)-substituted pyrazole, reaction of 5-metalled-N_1-protected pyrazoles with electrophiles represents an attractive alternative,[2] despite the unavoidable sequence of protection-deprotection steps. In this light, the [1+4] Beam's approach based on reaction of lithiated ketone hydrazones with aromatic esters[3] is appreciable for its synthetic efficacy, notwithstanding the limits implicit in the use of a strongly basic reagent.

In this Letter, we describe a novel, one-pot synthesis of 3(5)-substituted pyrazoles from aldehydes and diethoxyphosphorylacetaldehyde tosylhydrazone **1** which should validly complement the known methodologies.



1

Tosylhydrazone **1** was prepared[4] in one step from commercially available diethoxyphosphoryl acetaldehyde diethyl acetal.[5] Metallation of **1** in THF solution with 2 equiv NaH at 0°C produced a slightly yellow suspension of the corresponding dianion, which underwent Horner-Emmons reaction at room temperature with a variety of aldehydes to afford the N-sodium salt of α,β-unsaturated tosylhydrazones **2**.[6] Importantly, the electron withdrawing character of diethoxyphosphoryl group is essential to impart an unusual thermal stability to tosylhydrazone dianion. Thus, Shapiro decomposition[7] was not observed at 0°C, 1h in THF, and proceeded only very partially at room temperature (5% after 3 h).

Cyclization of **2** with release of sodium *p*-toluenesulphinate was observed to occur upon setting the reaction mixture to reflux, ultimately producing the title pyrazoles **3** in good yield.[8]

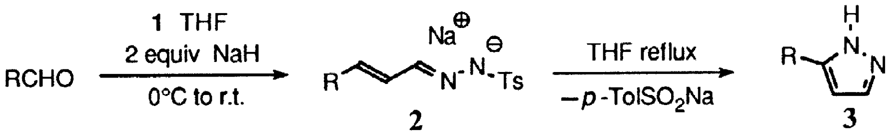


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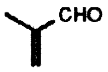
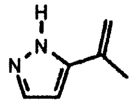
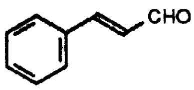
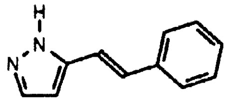
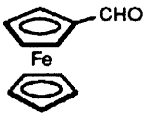
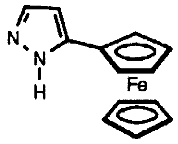
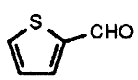
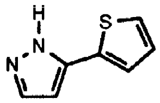
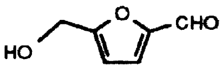
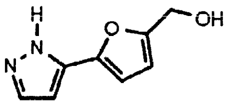
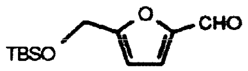
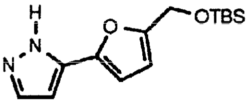
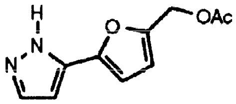
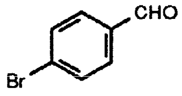
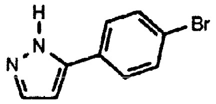
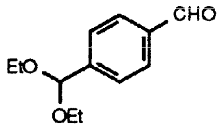
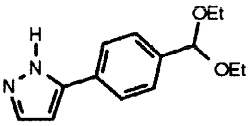
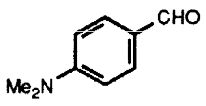
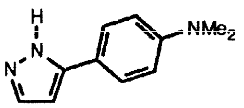
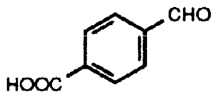
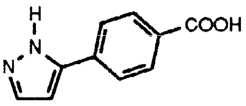
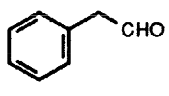
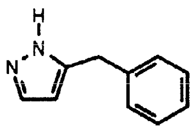
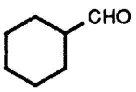
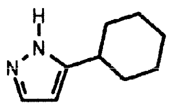
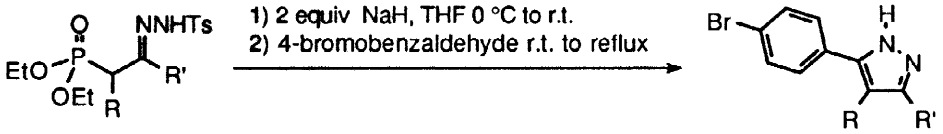
Table: Synthesis of 3(5)-Substituted Pyrazoles by Reaction of the Dianion of **1** with Aldehydes

Parent aldehyde[9]	Rxn time (h) 1st / 2nd step[a]	3(5)-Substituted pyrazole[10]	Yield[b] (%)	mp (°C)
	1.5 / 2		71	oil Ref. 11
	1 / 1		76	108-110 lit. 111[12]
	1 / 1		85	145-146 lit. 148-149[13]
	1 / 1		84	111-112 lit. 111-113[14]
	1.5 / 1.5		60	148-152[c]
	1.5 / 1		78	68-71[d]
	2 / 1		67	110-111[e]
	1 / 1		70	127-131 lit. 130-132[15]
	1 / 1		85	oil
	1.5 / 1		72	159-161[f]
	1 / 1		90[g]	>250[h]
	1 / 4		62	oil Ref. 2a
	1.5 / 5		64	oil Ref. 16

[a] 1st step and 2nd step (see text) were conducted in THF at room and reflux (65 °C) temperature, respectively. [b] Isolated yield. [c] Crystall. from acetone. [d] Crystall. from *n*-hexane. [e] Crystall. from EtOAc/*n*-hexane. [f] Crystall. from EtOAc. [g] Run in DMF, using 1.1 equiv. of 1 and 3.2 equiv. of NaH. [h] Crystall. from EtOH.

From the summary of examples presented in the Table, the method appears to be quite general. The reaction conditions leave a number of functional groups unscathed, and can be successfully applied to enolizable as well as unsaturated or aromatic aldehydes.

Two further examples anticipate the applicability of the present methodology to the concise synthesis of polysubstituted pyrazoles, and emphasizes the convergence and generality of the route.



R : Me, R' : H — 80% yield
mp 133-134 °C (from EtOAc / *n*-hexane)

R : H, R' : Me — 77% yield
mp 150-152 °C (from EtOH / H_2O)

In summary, by utilising the novel, bifunctional phosphonate **1** we have developed a new, one-pot route to 3(5)-substituted-1H-pyrazoles from aldehydes which stands as the first example of this kind of transformation. The tolerance towards various functional groups and the operational simplicity of the methodology make it a practical and efficient method for the synthesis of pyrazoles.

Representative procedure. To a THF (3.0 mL) suspension of NaH (65% in mineral oil, 0.165 g, 4.4 mmol) a solution of diethoxyphosphorylacetaldehyde tosylhydrazone **1** (0.750 g, 2.2 mmol) in the same solvent (4.0 mL) was added over five minutes at 0-5°C. After stirring for 30 min, the resulting yellow suspension was treated with a THF solution (3.0 mL) of the aldehyde (1.5 mmol). Stirring was continued for the indicated time (see Table, 1st step) at room temperature before bringing the mixture to reflux. After completion of the cyclization step (see Table, 2nd step), the reaction mixture was poured into 5% aq. NaH_2PO_4 and extracted with EtOAc. The crude product was then purified by chromatography on silica gel.

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4. A mixture of diethoxyphosphorylacetaldehyde diethyl acetal (11.30 mL, 46.8 mmol) and *p*-toluenesulphonhydrazide (8.27 g, 44.4 mmol) in 0.1 M hydrochloric acid (20 mL) was vigorously stirred at 63-65°C (internal temperature) for 2 hours. Upon cooling to room temperature, a solid precipitated in crops. After filtering, washing with water (25 mL) and diethyl ether (2 x 25 mL) the resulting white solid

was dried under reduced pressure for 20 hours to give 12.1-13.0 g (78-85% yield) of diethoxyphosphorylacetaldehyde tosylhydrazone 1 (95:5 mixture of *anti* /*syn* isomers, fast isomerization was observed in $CDCl_3$ and on silica gel), mp 105-106°C. ^{1}H-NMR (MeOD, 300 MHz): d 7.76 (2H, brd, J=8.1 Hz), 7.38 (2H, d, J=8.1 Hz), 7.13 (1H, brq, J=6.3 Hz), 6.90 (4H, quint., J=6.9 Hz), 2.84 (2H, dd, J=21.8, 6.3 Hz), 2.42 (3H, s), 1.20 (6H, t, J=6.9 Hz). Anal. Calcd for $C_{13}H_{21}N_2O_5PS$: C 44.82, H 6.08, N 8.04, P 8.89, S 9.20. Found C 44.95, H 6.14, N 8.04, P 9.01, S 9.17.

5. Alternatively, diethoxyphosphorylacetaldehyde diethyl acetal can be prepared from bromoacetaldehyde diethyl acetal according to Nagata, W.; Wakabayashi, T.; Hayase, Y. *Org. Synth. Coll. Vol. 6*, **1988**, 448-451.
6. In the case of cyclohexanecarboxaldehyde and 4-bromobenzaldehyde, the corresponding α,β-unsaturated tosylhydrazones were isolated upon acidic work up and characterised as a 70:30 and 96:4 *E/Z* mixture of isomers. Analysis of the cyclization course for the (*Z*)-cyclohexaneacrylaldehyde tosylhydrazone revealed no pyrazole formation under the condition described.
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8. The behaviour of open-chain, β-monosubstituted α,β-unsaturated tosylhydrazones towards bases has not been exaustively examined and results tend to be inconsistent. Isolated examples of cyclization to pyrazoles can be found in: (a) Dornow, A.; Bartsch, W. *Justus Liebigs Ann. Chem.* **1957**, *602*, 23-36; (b) Closs, G.L.; Closs, L.E.; Böll, W.A. *J. Am. Chem. Soc.* **1963**, *85*, 3796-3800; (c) Dürr, H. *Chem. Ber.* **1970**, *103*, 369-379; (d) Grandi, R.; Masserotti, W.; Pagnoni, U.M.; Trave, R. *Chim. Ind. (Milan)* **1977**, *59*, 56; (e) El-Youssoufi, J.; Lepage, L. *Bull. Soc. Chim. Fr.* **1994**, *131*, 48-52. On the other hand, carbene formation with cyclization to cyclopropene seems to be a viable and often important alternative: (f) Büchi, G.; White, J.D. *J. Am. Chem. Soc.* **1964**, *86*, 2884-3887; (g) Klicic J.; Rubin, Y.; Breslow, R. *Tetrahedron*, **1997**, *53*, 4129-4136. Moreover, treatment of cynnamaldehyde tosylhydrazone with methyllithium produced only extensive decomposition: (h) Dauben, W.G.; Lorber, M.E.; Vietmeyer, N.D.; Shapiro, R.H., Ducan, J.H.; Tomer, K. *J. Am. Chem. Soc.* **1968**, *90*, 4762-4763.
9. Parent aldehydes are commercial products with the exception of 5-(acetoxymethyl)furfural and 5-(TBDMSOmethyl)furfural which were prepared from the corresponding alcohol by usual methods.
10. All new compounds gave satisfactory spectral and elemental analysis data.
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