

ALKYLATION OF ALDEHYDE OXIME DIANIONS

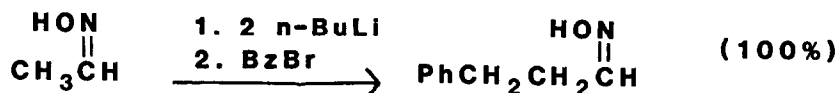
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Summary In contrast to an earlier report, aldoximes can be deprotonated to their dianions and alkylated in high yield.

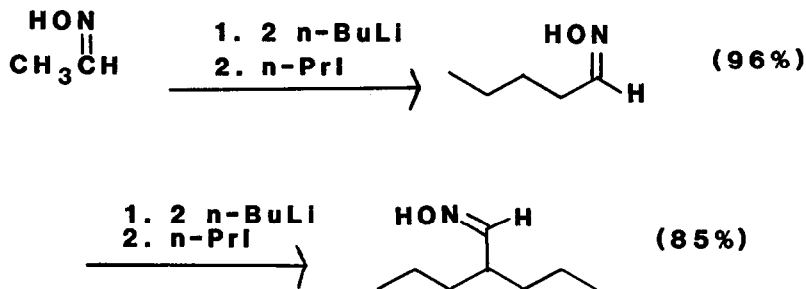
In 1976, Kofron¹ and Jung² reported that ketone oximes could be deprotonated and alkylated regioselectively syn to the oxime hydroxyl. In his report, Kofron noted that "attempts to alkylate acetaldehyde oxime gave no identifiable product." He further stated that propionaldehyde oxime could be alkylated in low yield, and that major byproducts appeared to be nitriles.¹ Because of our interest in studying aldoximes as substrates in the oxime rearrangement cyclization,³ we undertook a reinvestigation of aldoxime alkylation.

Observation of nitriles in Kofron's examples suggests kinetic deprotonation of the aldehydic hydrogen and expulsion of hydroxide. We find that by conducting the metallation at -78°C (Kofron's deprotonations were done at room temperature), dianion formation occurs readily. For example, treatment of 0.5 g acetaldehyde oxime⁴ in THF with 2.0 equivalents of n-butyl lithium (dropwise) at -78°C , followed by warming to 0° for 20 minutes, afforded the dianion. Quenching (at -78°C) with 1.0 equivalents of benzyl bromide and warming to room temperature for 1 hour, followed by aqueous workup and ether extraction afforded Z-3-phenylpropionaldehyde oxime in quantitative yield:



Knowing that oxime monoanions are deprotonated regioselectively syn to the oxime oxygen and that the thermodynamic mixture of acetaldehyde oxime diastereomers is only $61 \pm 5\%$ Z⁵, we were startled by the high yield. Evidently the oxime fractionally crystallizes in the Z form on storage at 0°C . Commercial samples⁴ of acetaldehyde oxime from two different lots, which had been refrigerated for several months, showed Z/E ratios of between 10 and 20 to 1, within the error limits of integration.⁵ Equilibrium is reached within 3 hours in benzene solution at 25°C , so the aldoxime solution must be cooled promptly.

A similar procedure was used to alkylate acetaldehyde oxime dianion with 1-iodopropane, affording Z-pentanaldehyde oxime in 96% yield. This product could be further alkylated (after workup but without delay) with a second equivalent of 1-iodopropane affording heptane-4-carboxaldehyde oxime in 85% yield:⁶



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FOOTNOTES

1. W.G. Kofron and M. K. Yeh, *J. Org. Chem.*, 41, 439-442 (1976).
2. M.E. Jung, P.A. Blair, and A. Lowe, *Tetrahedron Lett.*, 1439-1442 (1976).
3. a) R.E. Gawley, E.J. Termine, and K.D. Onan, *J. Chem. Soc., Chem. Commun.*, 568-569 (1981); b) R.E. Gawley and E.J. Termine, *Tetrahedron Lett.*, 23, 307-308 (1982); c) S. Sakane, Y. Matsumura, Y. Yamamura, Y. Ishida, K. Maruoka, and H. Yamamoto, *J. Amer. Chem. Soc.*, 105, 672-674 (1983).
4. Aldrich Chemical Co.
5. Karabatsos, G.J., And Taller, R.A., *Tetrahedron*, 24, 3347-3360 (1968).
6. Satisfactory analytical data have been obtained for all compounds.

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