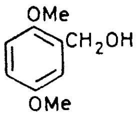
2,5-Dimethoxybenzyl Alcohol: a Convenient Self-indicating Standard for the Determination of Organolithium Reagents

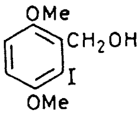
By Mark R Winkle, Janet M Lansinger, and Robert C Ronald*
(*Department of Chemistry, Washington State University, Pullman, Washington* 99164)

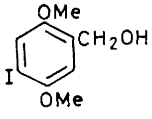
Summary A method for the determination of organolithium reagent is described using 2,5-dimethoxybenzyl alcohol as a self-indicating primary standard

---

As a part of some synthetic studies directed toward the total synthesis of the novel antibiotic frustulosin,[1] we have investigated the metallation of 2,5-dimethoxybenzyl alcohol (**1**) with various commercially available organolithium reagents, and have observed unusual behaviour in the reaction of (**1**) that we have adapted for the routine standardization[2] of commercial alkyl- and aryl-lithium reagents


(1)


(2)


(3)

When solutions of (**1**) in ether, tetrahydrofuran (THF), or benzene are treated with organolithium reagents, the initial reaction produces a colourless solution of the alkoxide, but when the deprotonation of the hydroxy group is complete the organolithium reagent reacts to form a mixture of intensely coloured red dianions of (**1**) The development of this colour at the endpoint appears to be instantaneous and requires less than 0 01 mmol equiv excess of organolithium reagent to be visible

The appearance of the red colour at the endpoint is not affected by the condition of the organolithium solution being titrated, even solutions that were highly discoloured or which contained large amounts of suspended oxides gave easily visible and reproducible endpoints In a typical titration a small amount of (**1**) (100—200 mg) was weighed into a small flask fitted with a magnetic stirrer and sealed with a septum The flask was flushed with nitrogen and the alcohol was dissolved in 1–4 ml of the appropriate solvent (THF, ether, or benzene) The organolithium reagent was added dropwise with a syringe until the solution was just charged with a pink colour The results of titrating various lithium reagents are summarized in the Table

TABLE Titration of organolithium reagents

Reagent	Nominal value[a]	Method A[b]	Method B[c]
$\mathrm{Bu^{n}Li}$	2 0 M	1 80 M	1 81 M
$\mathrm{Bu^{s}Li}$[d]	1 2 M	1 41 M	1 43 M
$\mathrm{Bu^{t}Li}$[e]	1 97 M	1 75 M	1 77 M
$\mathrm{Bu^{t}Li}$[f]	1 90 M	1 66 M	1 74 M
PhLi	1 7 M	1 06 M	1 09 M

[a] Nominal value from manufacturer (Ventron Corporation) [b] 2 5 Dimethoxybenzyl alcohol method [c] 1 10 Phenanthroline–$\mathrm{Bu^{s}OH}$ method [d] This sample was extremely cloudy and discoloured a Gilman double titration (ASTM E233–68) showed total base 1 90 M s butyl lithium 1 43 M other alkaline materials 0 47 M [e] Titration in benzene [f] Titration in THF

The origin of the red colour is uncertain, but it appears to be due to the presence of dianions in the solution Treatment of (**1**) with an excess of butyl-lithium results in an increase in colour proportional to the amount added until 2 equiv are added When the deep red dianion is quenched, the fading of the colour is also proportional to the amount of quenching agent added This behaviour seems to support the hypothesis that coloured product is a major component of the mixture and is not a trace contaminant Furthermore the development of the colour appears to be independent of the state of purity of (**1**), old, discoloured samples of (**1**) produce colour reactions identical to those observed with freshly chromatographed and distilled samples

Analysis of the products of the quenching of the dianion solution with D_2O or ethylene iodochloride has afforded only products from ring metallation One possible explanation for the red colour was the formation of an α-benzyloxy dianion However, we have been unable to find convincing evidence for the deprotonation of the benzyl group either by quenching with D_2O or by quenching the dianion formed from (**1**) (which was deuteriated in the benzyl position) with H_2O By quenching the dianion solution with ethylene iodochloride two iodides (**2**) and (**3**) have been isolated in 35 and 27% yields, respectively Treatment of these iodides with butyl-lithium to produce the dianions by halogen–metal exchange also affords red solutions albeit with somewhat lower intensity than that observed for solutions obtained by direct metallation

As a primary standard for the determination of organolithium reagents (**1**) has several advantages The organolithium reagent is added *via* a syringe to the alcohol (**1**) in the way it is usually used in most reactions, not in the reverse order of first adding the lithium reagent, thus the titre determined is for organolithium added in small portions to the solution Since (**1**) is quite soluble in a variety of solvents the titre can be conveniently determined in the reaction solvent We have observed, for example, some differences in the titre of t-butyl-lithium depending upon the solvents employed (see Table) The low titre for t-butyllithium in THF is due to the reactivity of this solvent [3] Furthermore, (**1**) is readily available (Aldrich) and easily purified Small amounts may be conveniently purified by bulb-to-bulb distillation at 100 °C and 0 05 mmHg just prior to titration, thus ensuring that the standard is dry and free from impurities, although we have obtained equally good results with undistilled material

(*Received*, 21*st September* 1979, *Com* 1017)

---

[1] R C Ronald and J M Lansinger *J C S Chem Comm* 1979 124

[2] S C Watson and J F Eastham *J Organometallic Chem* 1967 **9** 165 H Gilman and F K Cartledge *ibid* 1964 **2** 447, W C. Kofron and L M Baclanski *J Org Chem* 1976 **41** 1879 L Duhamad and J -C Plaquevent *ibid* 1979 **44** 3404, see also T R. Crompton Chemical Analysis of Organometallic Compounds Academic Press New York 1973 vol 1 ch 1

[3] B J Wakefield 'The Chemistry of Organolithium Compounds, Pergamon, Oxford, 1974 p 199