

## Novel Regioselective Generation of Nitroalkane Dianions

Kazutoshi Yamada,\* Seiji Tanaka, Shigeo Kohmoto, and Makoto Yamamoto

Department of Industrial Chemistry, Faculty of Engineering Chiba University, 1-33 Yayoicho Chiba-shi, 260 Japan

An alteration of the regioselectivity in dianion formation, from the usual  $\alpha,\alpha$ -dianions to the uncommon  $\alpha,\beta$ -dianions, of nitroethane and 1-nitropropane was established by changing the order of addition of reagents.

Regioselective C–C bond formation by the reaction of polyanions with electrophiles is interesting with respect to new synthetic methods.<sup>1</sup> Recently, Seebach *et al.*<sup>2</sup> have made improvements in the Henry reaction and emphasized the usefulness of nitro compounds for regio- and stereo-selective C–C bond formation. However by their double deprotonation method, the formation of  $\alpha,\beta$ -dianions was limited to secondary and  $\beta$ -aryl nitroalkanes.<sup>3</sup> From primary nitroalkanes,  $\alpha,\alpha$ -dianions (**1**) were prepared regiospecifically in all cases except one.<sup>4</sup> We were interested in this relatively unexplored regioselective generation of  $\alpha,\beta$ -dianions of primary nitroalkanes (**2**) in connection with our investigation on the photochemistry of nitronate anions<sup>5</sup> and nitroalkane dianions. The solvent addend hexamethylphosphoric triamide (HMPA) is known to play an important role in changing the regioselectivity of anion formation<sup>6</sup> and also in affecting the ratio of *E/Z* enolate anion formation by changing the addition sequence of the base. We, hence, re-examined Seebach's double deprotonation technique considering the above points. The change of the addition sequence of reagents showed an interesting alteration of regioselectivity in dianion formation.

Following Seebach's procedure<sup>8</sup> (procedure A) nitroethane dianion was added to benzaldehyde, *i.e.*, Bu<sup>n</sup>Li (22 mmol) was added to a tetrahydrofuran (THF) solution of nitroethane (11 mmol) and HMPA (56.9 mmol) at  $-90^\circ\text{C}$  and then benzaldehyde (10 mmol) was added. The  $\alpha$ -type product (**3**)<sup>9</sup> derived from the  $\alpha,\alpha$ -dianion predominated over the  $\beta$ -type product (**4**)<sup>†</sup> derived from the  $\alpha,\beta$ -dianion [(**3**):(**4**) 85:15]. With the same molar ratio and temperature, but changing the sequence of addition, *i.e.*, addition of nitroethane to a THF

solution of Bu<sup>n</sup>Li and HMPA (procedure B), followed by addition of benzaldehyde led to (**4**) almost exclusively [(**3**):(**4**) 5:95] with a total yield of 76%. Also remarkable was the effect of the solvent addend HMPA; a control reaction using procedure B without HMPA gave (**3**) as a single product. The ratio of HMPA to Bu<sup>n</sup>Li was also found to direct the regioselectivity. A ratio of HMPA to Bu<sup>n</sup>Li of <1:1 showed a preference for (**3**) while (**4**) dominated at a ratio >2:1. Procedure A did not demonstrate such an effect. However the ratio of epimers (*threo/erythro*) was affected as reported.<sup>8</sup>

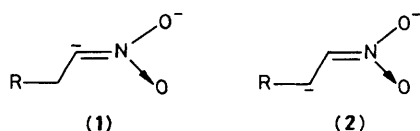
This effect of HMPA was further investigated in the reaction of nitroethane dianion with benzyl bromide by procedure B, which showed a similar tendency to that observed in the reaction with benzaldehyde. Virtually exclusive formation of the  $\beta$ -type product (**6**)<sup>10</sup> was observed for HMPA: Bu<sup>n</sup>Li = 2, though the yield was low (~30%).

To extend the scope of this methodology, the reaction of nitroethane dianion generated by procedure B was also carried out with electrophiles: hexanal, cyclohexanone, and benzophenone. In all cases,  $\beta$ -type products predominated with 99% regioselectivity, and isolated yields of 35, 63, and 18% respectively. § 1-Nitropropane showed a similar 99%

Table 1. Effect of HMPA on the ratio of (**3**) to (**4**) by procedure B.<sup>a</sup>

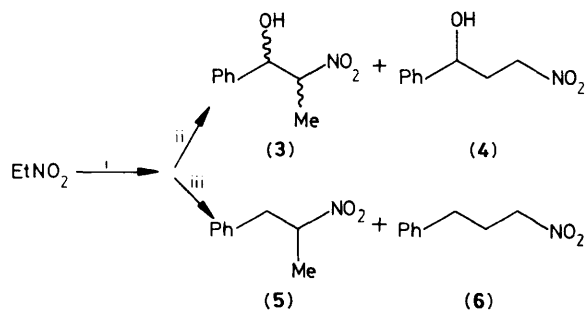
HMPA /Bu <sup>n</sup> Li <sup>b</sup>	( <b>3</b> ):( <b>4</b> )	Yield, % <sup>c</sup>
0	100:0	57
0.78	84:16	62
1.55	70:30	60
2.10	11:89	57
2.60	5:95	76

<sup>a</sup> Nitroethane was added at  $-90^\circ\text{C}$  and the temperature was raised to  $-78^\circ\text{C}$  when benzaldehyde was added. The temperature was then quickly raised to  $-35^\circ\text{C}$ . <sup>b</sup> Molar ratio. <sup>c</sup> Total isolated yield.



† Compound (**4**) was hydrogenated to a known amine.

§ All new compounds gave satisfactory <sup>1</sup>H n.m.r. and mass spectra, and elemental analyses.



Reagents: i,  $\text{Bu}^n\text{Li}/\text{HMPA}$ ; then ii,  $\text{PhCHO}$ ; or iii,  $\text{PhCH}_2\text{Br}$ .

$\beta$ -selectivity (isolated yield, 77%) in the reaction with benzaldehyde.<sup>§</sup>

Attempts to differentiate between kinetic or thermodynamic control of this regioselectivity were not conclusive.<sup>‡</sup> To the best of our knowledge, the present finding is the first example of the alteration of regioselectivity in dianion formation as a function of the amount of HMPA. The sequence of additions is the practical key factor to facilitate this interesting regioselectivity, which has a wide synthetic potential.

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<sup>‡</sup> Dianions were prepared at  $-80$  to  $-30^\circ\text{C}$ .

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