# Synthesis of γ-Cyanoaldehydes: Conjugated Addition of Lithiated Anions of Arylacetonitriles to αβ-Unsaturated Aldehydes and Imines

By MAHMOUD EL BOUZ, MARIE-CLAUDE ROUX-SCHMITT, and LYA WARTSKI
(*Groupe de Recherche No.* 12 *C.N.R.S.*, 2—8 *Rue Henri Dunant, B.P.* 28, 94320 *Thiais, France*)

*Summary* γ-Cyanoaldehydes may be synthesized by the reaction of lithiated arylacetonitriles with either αβ-unsaturated aldehydes or αβ-unsaturated imines.

ALTHOUGH 1,4 addition to α-enones can be easily achieved, 1,2 addition is generally observed with αβ-unsaturated aldehydes, even if cuprate reagents are used,[1] although there are some exceptions to this.[2] Recently, Michael addition of malonates and acetoacetates to αβ-unsaturated aldehydes has been performed under phase-transfer catalysis conditions;[3] however, with cyanoacetic esters 1,4 addition does not take place and only Knoevenagel condensation is observed.[3] Under conditions under which the lithiated anions derived from arylacetonitriles undergo 1,4 addition to α-enones [tetrahydrofuran–hexamethylphosphoric triamide (THF–HMPA) at −70 °C] we have recently shown that a competitive 1,2 addition occurs with aldehydes.[4] However, it is possible that 1,4 addition would be favoured by using THF alone at higher temperatures, as the formation of 1,2-addition products should be reversible.[5] 1,4 Addition to αβ-unsaturated aldehydes *via* αβ-unsaturated imines has been realized using malonates and organomagnesium compounds by Yamada[6] and cyanated organoaluminium compounds by Nagata;[7] a few examples of 1,4 addition to aldimines have been described by Miginiac.[8]

We now report two convenient one-pot methods for the synthesis of γ-cyanoaldehydes involving the reaction of lithiated arylacetonitriles with either αβ-unsaturated aldehydes (method A) or αβ-unsaturated imines (method B), followed by hydrolysis of the crude product.

In method A, the reactions were carried out in THF at −70 °C for 30 min, followed by stirring at −30 to 0 °C for 2—3 h. After hydrolysis with 10% aqueous HCl, extraction with diethyl ether, and work-up the crude product was analysed by n.m.r. spectroscopy and purified by t.l.c. on neutral alumina. In method B, the reactions were performed at −70 °C in THF–HMPA (80:20) for 5—6 h, followed by stirring at room temperature for 12 h. Saturated cold aqueous $NH_4Cl$ was then added and the mixture was extracted with diethyl ether. The ethereal solution was stirred at 0 °C with aqueous AcOH–AcONa by the method of Schlessinger[9] and after work-up the crude product was analysed by n.m.r. spectroscopy and purified by t.l.c. on neutral aluminina.

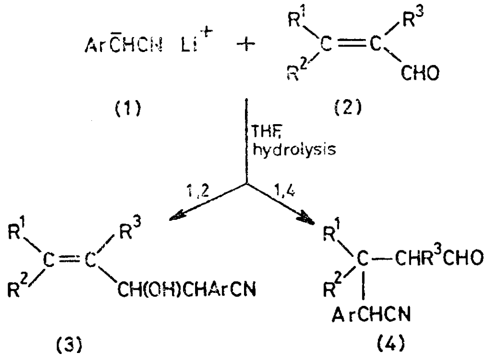
TABLE. 1,4 addition of (**1**) to $\alpha\beta$-unsaturated aldehydes (**2**) (method A) and $\alpha\beta$-unsaturated imines (**5**) (method B).[a]

| | | | | | % Yield of (**4**) | |
|---|---|---|---|---|---|---|
| Expt. | Ar | $R^1$ | $R^2$ | $R^3$ | Method A | Method B |
| 1 | $p$-MeOC$_6$H$_4$ | Me | H | H | 60[b] | 90 |
| 2 | Ph | Me | H | H | 60[b] | 80 |
| 3 | $m$-ClC$_6$H$_4$ | Me | H | H | 70 | 70 |
| 4 | $p$-MeOC$_6$H$_4$ | Ph | H | H | 70 | 70 |
| 5 | Ph | Ph | H | H | 60 | 75 |
| 6 | $m$-ClC$_6$H$_4$ | Ph | H | H | 70 | 10[b] |
| 7 | $p$-MeOC$_6$H$_4$ | Me | Me | H | 80 | 30[b] |
| 8 | Ph | Me | Me | H | 65 | 10[b] |
| 9 | $m$-ClC$_6$H$_4$ | Me | Me | H | 85 | — |
| 10 | $p$-MeOC$_6$H$_4$ | H | H | Me | 70 | — |
| 11 | Ph | H | H | Me | 75 | — |
| 12 | $m$-ClC$_6$H$_4$ | H | H | Me | 75 | — |

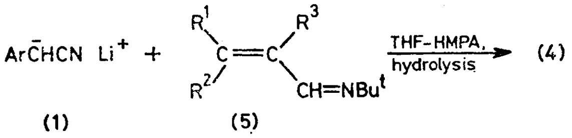
[a] All the products were identified by i.r., n.m.r., and mass spectroscopy. Yields of (**4**) were calculated by $^1$H n.m.r. integration of the C*H*O protons, internal standard aromatic protons for method A and $p$-NCC$_6$H$_4$C*H*O proton for method B. [b] Arylacetonitrile and $\alpha\beta$-unsaturated aldehyde were detected as well as polymeric material.

The results (Table) show that conjugated addition of lithiated anions from arylacetonitriles (**1**) to $\alpha\beta$-unsaturated aldehydes (**2**) (method A) gives good yields of $\gamma$-cyanoaldehydes (**4**) in all cases. However, with the $\alpha\beta$-unsaturated imines (**5**) (method B) the yields are good when $R^1$ = Me or Ph (expts. 1B—5B) except for expt. 6B with Ar = $m$-ClC$_6$H$_4$, but if the $\beta$ carbon atom of the imine is disubstituted the yields are poor (expts. 7B and 8B). This is in agreement with the results of Miginiac[10] *et al.* who were unable to obtain >50% yields in reactions of alkyl-, phenyl-, or alkenyl-lithium compounds with imines derived from mesityl oxide.

Method A



Method B



Experimentally, when $R^1$ = Me or Ph and $R^2$ = $R^3$ = H (expts. 1—5) it is easier to prepare the $\gamma$-cyanoaldehydes from imines (method B) as the amines resulting from 1,2 addition are soluble in aqueous acid. However, when $R^1$ = $R^2$ = Me and $R^3$ = H, only method A gives good yields of (**4**) (expts. 7—9). With $R^1$ = $R^2$ = H and $R^3$ = Me (expts. 10—12) only method A has been used, as in this case the corresponding imine (**5**) is difficult to synthesize in good yields. Methods A and B are thus complementary.

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