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A GENERAL SYNTHESIS OF 3-AMINO-2-ALKENENITRILES BY THE CROSS-THORPE REACTION

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Highly selective cross-Thorpe reaction is achieved between an α-lithioalkanenitriles and a protected cyanohydrin to give 4-alkoxy-4-amino-2-alkenenitrile, which, in turn, is converted by deprotection and acetylation followed by hydrogenolysis to 3-amino-2-alkenenitrile, a formal cross-Thorpe product.

The title compounds are versatile intermediates for the synthesis of such heterocycles as uracils,[1] imidazoles,[2] and others.[3] Although 3-amino-2-alkenenitriles are produced by the Thorpe reaction,[4] namely, condensation of two molecules of nitriles, the method is of no general use owing to oligomerization of the starting nitriles.[4c] Furthermore, proton abstraction by α-metaloalkanenitrile from the second nitrile takes place rapidly to yield complex mixture of products. Hence the cross-Thorpe reaction had no synthetic meaning. We have found that α-lithioalkanenitriles react efficiently with protected cyanohydrins to give the cross-Thorpe products.

Alkanenitriles (R^1CH_2CN) were lithiated by treatment with butyllithium in tetrahydrofuran (THF) at -78°C[5] to give α-lithioalkanenitriles (I) which were allowed to react with protected cyanohydrins (II) at the same temperature. Quenching the reaction mixture with aqueous ammonium chloride and extractive workup afforded 4-alkoxy-3-amino-2-alkenenitriles (III)[6] in good yields. Results are summarized in Table 1. With respect to the configuration of III the products generally consist of E/Z isomers as revealed by ^1H NMR spectra[6] except IIId and IIIe which were both isomerically pure. The configuration of these is assumed to be Z based on the steric bulk of $R^2R^3C(OR^4)$ moiety as well as the preferred intramolecular hydrogen bonding.[7] In contrast to 3-amino-2-alkenoate esters[7b] III are not readily hydrolyzed by silica gel TLC.

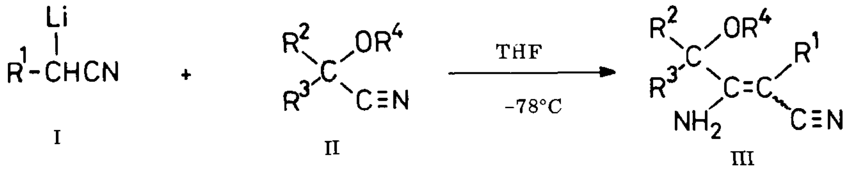
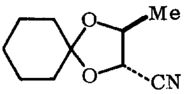
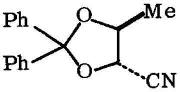
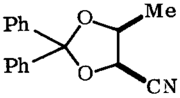


Table 1 Synthesis of 4-Alkoxy-3-amino-2-alkenenitriles (III)[a]

	R^1	R^2	R^3	R^4	Yield (%)[b] of III	Bp (°C/Torr) or mp (°C)
a	H	H	Me	Et	83	[d]
b	H	H	Me	EE[c]	87	120/0.1
c	H	H	Me	THP[c]	99	137/0.1
d	H	Me	Me	EE[c]	78	42-43
e	H	Me	OMe	Me	81	98-99
f	Et	H	Me	EE[c]	51	[e]
g	H			(IIg)[h]	78	137/0.1
h	H			(IIh)[h]	87	[f]
i	H			(IIi)[h]	99	[g]

[a] The reaction was carried out in 2 to 10 mmol scale.

[b] Isolated yields.

[c] EE: 1-ethoxyethyl, THP: tetrahydropyran-2-yl.

[d] Viscous oil, R_f 0.38 (silica gel TLC, hexane-ethyl acetate 1:1).

[e] Viscous oil, R_f 0.47 (silica gel TLC, hexane-ethyl acetate 1:1).

[f] Viscous oil, R_f 0.63 (silica gel TLC, hexane-ethyl acetate 1:2).

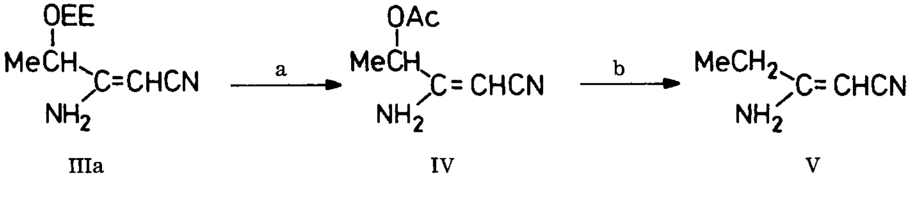
[g] Viscous oil, R_f 0.38 (silica gel TLC, hexane-ethyl acetate 1:1).

[h] Synthesis of this nitrile will be disclosed shortly.

We also observed that nitriles lacking the α-alkoxy substituent gave the cross-Thorpe product in lower yields. For example, the reaction of lithioacetonitrile with benzonitrile gave 3-amino-3-phenylpropenenitrile in 63% yield, whereas the reaction with isobutyronitrile afforded the desired product in 23% yield only and that with butyronitrile a mixture of four possible condensation products (totally 33% yield) due to the expected rapid proton abstraction. Thus, the presence of the α-alkoxy substituent is essential for the success of the cross-Thorpe reaction. Possibly, the alkoxy substituent coordinates the lithium ion of I to activate the carbanion and thus to facilitate the nucleophilic attack of the carbanion species to the nitrile carbon.

A typical experimental procedure is given for the preparation of IIIe. To a well-stirred solution of acetonitrile (0.41 g, 10 mmol) in THF (20 ml) was added dropwise the 1.6 mol/dm^3 hexane solution of butyllithium (6.3 ml, 10 mmol) at -78°C. The resulting turbid solution was stirred for 15 min at the same temperature, and then 2,2-dimethoxypropanenitrile (1.15 g, 10 mmol) was injected to the reaction mixture. The solution grew clear instantly and after 10 min was poured into aqueous ammonium chloride solution. Extraction with ether (3 times), washing the organic layer with brine, drying the ethereal layer over anhydrous sodium sulfate, filtration, concentration, followed by recrystallization from hexane, gave 4,4-dimethoxy-3-amino-2-pentenenitrile (IIIe) (1.26 g, 81% yield).[6]

The alkoxy substituent is reductively removed easily. For example, the ethoxyethyl protecting group of IIIa was removed with pyridinium p-toluenesulfonate in refluxing methanol. Acetylation of the resulting hydroxyl group (Ac_2O, Py, r.t.) gave IV[9] in 57% yield which was subjected to hydrogenolysis (10% Pd/C, EtOH, r.t., 1 atm H_2) to give 3-amino-2-pentenenitrile V (70% yield).[10] This product is, in total transformation, a cross-Thorpe product between lithioacetonitrile and propionitrile.



a: (i) MeOH, $PyH^+ TsO^-$, reflux, (ii) Ac_2O, Py

b: 10% Pd/C, H_2 (1 atm), EtOH, r.t.

References and Notes

1. M. Ohoka, S. Yanagida, and S. Komori, J. Org. Chem., 37, 3030 (1972).
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3. (a) D. J. Brown and K. Tenega, J. Chem. Soc., Perkin Trans. 1, 372 (1974). (b) H. E. Schroeder and G. W. Rigby, J. Am. Chem. Soc., 71, 2205 (1949).

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5. E. M. Kaiser and C. R. Hauser, J. Org. Chem., **33**, 3402 (1968).
6. IIIa: IR (neat) 3470, 3360, 3245, 2195, 1630, 1590 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.20 and 1.36 (t and s, combined 6 H), 3.40 and 3.43 (2 q, combined 2 H), 3.77 and 3.84 (2 s, combined 1 H), 4.1-4.6 (m, 1H), 5.0 and 5.3 (2 br, combined 2 H). IIIb: IR (neat) 3470, 3350, 3240, 2190, 1630, 1590 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.1-1.6 (m, 9 H), 3.3-3.6 (m, 2 H), 3.74 and 3.78 (2 s, combined 1 H), 3.9-4.3 (m, 1 H), 4.5-4.8 (m, 1 H), 4.9-5.1 (2 br, combined 2 H). IIIc: IR (neat) 3450, 3340, 3230, 2180, 1625, 1580 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.3-2.0 (m, 9 H), 3.2-5.4 (m, 7 H). IIId: IR (KBr) 3440, 3365, 3255, 2195, 1645, 1585 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.14 and 1.27 (t and d, combined 6 H), 1.41 (s, 6 H), 3.42 (q, 2 H), 3.80 (s, 1 H), 4.69 (q, 1 H), 5.2 (br, 2 H). IIIe: IR (KBr) 3445, 3340, 3250, 2185, 1625, 1585 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 1.46 (s, 3H), 3.20 (s, 6 H), 4.18 (s, 1 H), 5.1 (br, 2 H). IIIf: IR (neat) 3480, 3360, 3250, 2180, 1625 cm^{-1}; ^{1}H NMR (CCl$_4$) δ 0.9-1.6 (m, 12 H), 1.98 (q, 2 H), 3.3-3.8 (m, 2 H), 4.3-4.7 (m, 4 H). IIIg: IR (neat) 3480, 3350, 3230, 2190, 1625, 1585 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.1-1.8 (m, 13 H), 3.7-4.1 (m + 2 s (δ 3.84 and 3.89), 2 H), 4.53 (d, 1 H), 4.8 and 5.1 (2 br, 2 H). IIIh: IR (neat) 3490, 3400, 3255, 2200, 1635, 1595 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.1-1.6 (m, 3 H), 3.78 (s, 1 H), 3.9-4.2 (m, 2 H), 4.6-5.0 (br, 2 H), 6.8-7.6 (m, 10 H). IIIi: IR (neat) 3480, 3390, 3260, 2195, 1635, 1590 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.2-1.5 (m, 3 H), 3.77 (s, 1 H), 3.9-4.5 (m, 2 H), 4.7-5.1 (br, 2 H), 7.1-7.6 (m, 10 H).
7. (a) D. J. Aberhart and H.-J. Lin, J. Org. Chem., **46**, 3749 (1981). (b) T. Hiyama and K. Kobayashi, Tetrahedron Lett., **23**, 1597 (1982).
8. Lithioacetonitrile failed to react with α-methoxyphenylacetonitrile and methoxyacetonitrile due probably to rapid proton abstraction from these nitriles.
9. R$_f$ 0.47 (hexane-ethyl acetate 1:1); IR (neat) 3455, 3360, 3240, 2190, 1735, 1640, 1595 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.48 and 1.55 (2 d, combined 3 H), 2.10 and 2.19 (2 s, combined 3 H), 3.99 and 4.10 (2 s, combined 1 H), 4.6 and 4.9 (2 br, combined 2 H), 5.14 and 5.23 (2 q, combined 1 H).
10. R$_f$ 0.86 (hexane-ethyl acetate 1:1); IR (neat) 3450, 3355, 3245, 2180, 1635, 1585 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.13 and 1.22 (2 t, combined 3 H), 2.13 and 2.42 (2 q, combined 2 H), 3.81 and 4.03 (2 s, combined 1 H), 4.2-5.1 (br, 2 H).

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