Polymer-Supported α-Aminonitriles: Alkylation Reactions and Carbonyl Compound Cleavage

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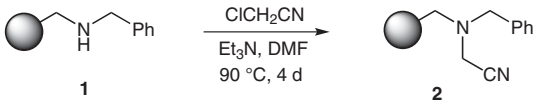
Abstract: A polystyrene-supported α-aminonitrile has been prepared and its successive mono- and dialkylations achieved. Complementary procedures allow cleavage of the alkylated moities in either carbonyl or acetal form.

Key words: aminonitriles, alkylations, solid-phase synthesis, cleavage, carbanions

α-Aminonitriles, first described by Strecker 160 years ago,[1] are today recognised as versatile synthetic intermediates displaying a wide array of synthetically useful chemical reactivities.[2] One of their important features is their ability to undergo deprotonation at the α-carbon centre followed by reaction of the anion with carbon electrophiles, permitting elaboration of the carbon skeleton prior to transformation of the aminonitrile function into an amino acid, diamine, or other functional group array. This chemistry provides an attractive route to structural diversity which has been exploited synthetically by a number of research groups,[3,4] and we have used this approach for the construction of a wide range of highly functionalised cyclopropanes.[5] One of the key reactions of aminonitriles was established in pioneering contributions by Hauser,[6] Büchi,[7] and Stork,[8] who demonstrated that a retro-Strecker reaction performed on an alkylated or dialkylated aminonitrile leads to the corresponding carbonyl compound. As such, deprotonated α-aminonitriles are formally acyl anion equivalents.

Solid-phase technology is a powerful technique for the rapid preparation of a diversity of small organic molecules.[9] Many of the commonly used polymer supports will tolerate the presence of carbanions, and a variety of solid-phase enolates have been generated from carbonyl compounds for alkylation or other carbon–carbon bond-forming reactions.[10–12] Curiously, however, very little work has been described concerning aminonitrile chemistry on the solid phase. Polymer-supported aminonitriles have served as intermediates for the preparation of a library of 2-pyrazinones,[13] while a solid-phase Strecker reaction has been used as a route to selected aminoacids.[14] In an elegant solid-supported synthesis of saframycin A analogues, Myers[15] used a Lewis acid catalysed aminonitrile translocation strategy for the cyclo-release step. To our knowledge, only one successful alkylation of solid-supported aminonitriles has been described: polystyrene-bound Reissert compounds (i.e., *N*-acyl aminonitriles) were alkylated using strong base (LDA) and allylic electrophiles, and a 1,3-dipolar cycloaddition followed by Reissert hydrolysis provided substituted isoxazolinoisoquinolines.[16,17] Efforts to perform a polymer-bound version of the alkylation of Husson's CNRS synthon were reportedly unsuccessful.[18] In this letter, we present the first examples of solid-phase aminonitrile deprotonation–alkylation procedures and compare them with solution-phase reactions.

Benzylaminomethyl polystyrene **1**[19] was treated with an excess of chloroacetonitrile to give supported aminonitrile **2** (Scheme 1).[20] Combustion analysis of **2** showed that the nitrogen content had doubled, while HR-MAS NMR spectroscopic data indicated the presence of a CH_2CN function. An NF-31 test[21] was negative, which indicated no residual secondary amine functions.



1 2

Scheme 1 Preparation of the supported aminonitrile

The first series of experiments was conducted to determine the optimal conditions for monoalkylation. A known excess of LDA was added slowly to a cooled suspension of resin **2** in THF and a deep orange-pink coloration appeared. A known excess of benzyl bromide **4a** was then added, which returned the resin coloration to pale yellow. The mixture was finally quenched with aqueous NH_4Cl. To evaluate the extent of alkylation, the resins **5a** obtained from the above procedures were treated overnight with oxalic acid in a THF–water mixture to perform a retro-Strecker reaction;[22] direct analysis of the liquid-phase extracts by GC-MS indicated the content of phenylacetaldehyde **6a** and diphenylacetone **7a** (Table 1).

Several interesting points emerged from this optimisation study. With only 2 equivalents of LDA, deprotonation

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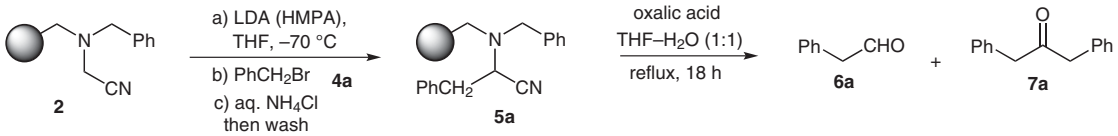
Table 1 Monobenzylation of Resin **2** in Different Conditions



Entry	LDA (equiv)[a]	HMPA (equiv)[a]	$PhCH_2Br$ (equiv)[a]	Content **6a** (%)[b]	Content **7a** (%)[b]
1	2	–	5	–[c]	–[c]
2	2	8	5	–[c]	–[c]
3	5	–	15	95	–[c]
4	5	20	15	65	–[c]
5	15	–	25	–	–
6	15	60	25	72	4
7	25	–	60	23	–[c]
8	25	100	60	43	5

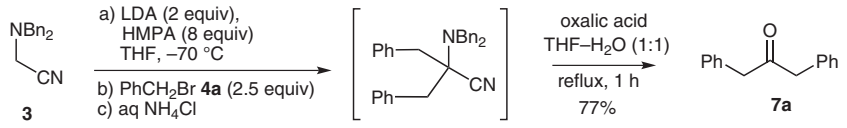
[a] Expressed relative to resin loading (0.57 mmol g^{-1}).
[b] Expressed as the percentage content of the crude cleaved material; determined by GC-MS (see ref. 24 for details).
[c] Not detected.

was inefficient; however 5 equivalents of the base gave a smooth monoalkylation, and these conditions were retained as standard for the next series of experiments. The use of larger amounts of base and electrophile did not produce significant changes. It was noteworthy that the formation of ketone **7a** was very low, which indicated that the one-pot double alkylation reaction was minimal, even in the presence of a large excess of reagents. This observation contrasts with solution-state behaviour. In the presence of 2 equivalents of LDA and 2.5 equivalents of benzyl bromide, aminonitrile **3** gave a dialkylated product which was not sufficiently stable to be purified, and was therefore hydrolysed with oxalic acid to give ketone **7a** in 77% overall yield (Scheme 2). HMPA did not have a beneficial effect on the benzylation of supported aminonitrile **2**.

A series of deprotonation–monoalkylation reactions was next performed under the standard conditions using different electrophiles **4** (Table 2).[23] The resulting alkylated resins **5a–d** were treated with oxalic acid to liberate the desired aldehyde **6**.[24] Iodooctane (**4b**) and geranyl bromide (**4c**) produced results comparable to that for benzyl bromide (**4a**), although the effects of the presence of HMPA during the deprotonation step were variable. No trace of a succinaldehyde dioxolane monoacetal (**6d**) was detected when 2-(2-bromoethyl)-1,3-dioxolane (**4d**) was used as the electrophile. A control reaction confirmed that this product is degraded by the oxalic acid cleavage conditions, so an alternative cleavage protocol was sought.

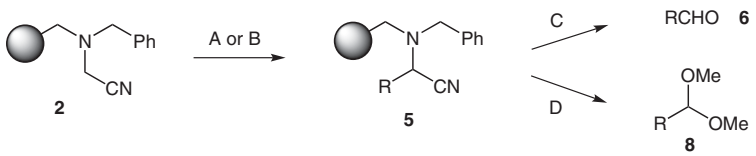
Efforts to induce mild hydrolytic cleavage of phenylacetaldehyde from resin **5a** using $AgNO_3$ in aqueous THF[3c,25] were hampered by the appearance of a dark coating (presumably AgCN) on the resin. The mild generation of carbonyl functions from aminonitriles using copper(II) sulfate pentahydrate in aqueous methanol was first proposed by Büchi,[7] and has been used successfully by various groups.[3k,8,26] Initial tests on resin **5a** indicated that exposure to a solution of $CuSO_4 \cdot 5H_2O$ in aqueous methanol liberated a mixture of **6a** and its dimethyl acetal **8a**. Use of a $CuSO_4 \cdot 5H_2O$ solution in dry methanol gave only the acetal **8a**, and it was found that pre-swelling of the resin in a few drops of DMF improved product recovery significantly. This procedure was therefore adopted for the cleavage of alkylated resins **5a–d** (Table 2).[27] Acetals **8a**, **8b**, and **8d** were thus obtained smoothly; the latter compound is notably a succinaldehyde protected by two different acetal groups. The geranyl derivative **8c**, however, appeared to have been degraded by this procedure.

Although Büchi alluded to acetal formation in a footnote,[7] aminonitrile methanolysis has not been previously described. We therefore checked that this procedure also works in solution state reactions the analogous nonsupported aminonitriles **9** (Table 3). As had been observed for resin **5c**, the geranyl derivative **9c** underwent degradation; otherwise the procedure appeared to constitute a di-

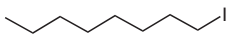
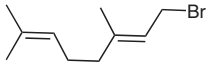
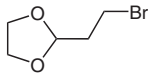


Scheme 2 One-pot double alkylation of aminonitrile **3**

Table 2 Monoalkylation of Resin **2** with Different Electrophiles[23]



A: a) LDA (5 equiv), THF, –70 °C, 2 h; b) electrophile **4** (15 equiv), 6 h; c) aq. NH_4Cl then wash
B: as for A, with HMPA (20 equiv) added to LDA
C: oxalic acid, THF–H_2O (1:1), reflux, 18 h
D: pre-swell in DMF, then $CuSO_4 \cdot 5H_2O$ in dry MeOH, reflux, 18 h

Entry	Electrophile **4**	**6** (A then C) purity (%)[a]	**6** (B then C) purity (%)[a]	**8** (A then D) purity (%)[a]
a		95	65	55
b		71	32	54
c		56	71	–[b]
d		–[b]	–[b]	55

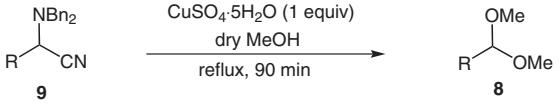
[a] Determined by GC-MS (see ref. 24 or 27 for details).
[b] Complex mixture obtained.

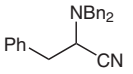
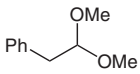
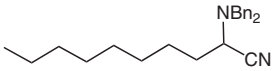
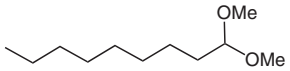
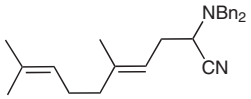
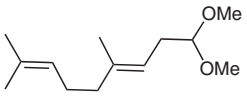
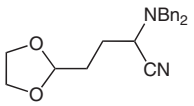
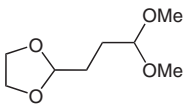
rect, one-pot transformation of aminonitriles **9** into acetals **8**.

We then turned our attention to the dialkylation of polymer-bound aminonitriles. Monobenzylated resin **5a** was subjected to a second alkylation protocol,[23] using the standard reagent proportions (5 equiv LDA, optional presence of 20 equiv HMPA, 15 equiv electrophile) for each of the three electrophiles **4a**–**c**. The resulting resins **10a**–**c** were washed and stocked; subsequent treatment with oxalic acid[24] allowed cleavage of the expected ketones **7** (Table 4). The second alkylation worked well for benzyl bromide **4a** and iodooctane **4b** but only if HMPA was present. In contrast, the absence of HMPA was actually beneficial for the procedure in the case of geranyl bromide **4c**. It is noteworthy that the intermediate dialkylated resins **10a**–**c** are stable versions of α,α-dialkylaminonitriles. Such compounds are often labile and readily undergo retro-Strecker processes to liberate ketones (e.g., vide supra, Scheme 2).

In summary, this study delineates the successful deprotonation–alkylation reactivity of polymer-bound aminonitriles. Treatment with an excess of LDA and an

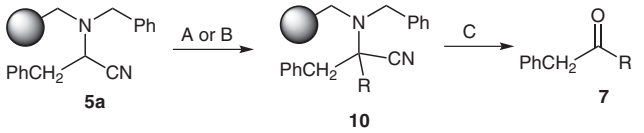
Table 3 One-Pot Methanolysis of Aminonitriles

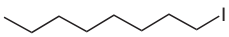
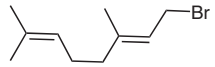


Entry	Aminonitrile **9**[a]	Product acetal **8**	Yield of **8** (%)
a			60
b			58
c			–[b]
d			57

[a] Prepared by alkylation (LDA/electrophile **4**) of *N*,*N*-dibenzylamino-acetonitrile (**3**) according to a standard procedure (ref. 5e).
[b] Extensive degradation.

Table 4 Second Alkylation of Resin **5a** with Different Electrophiles[a]



Entry	Electrophile **4**	Procedure A, **7** purity (%)[b]	Procedure B, **7** purity (%)[b]
a		–[c]	68
b		–[c]	73
c		42	24

[a] Reaction conditions: A: a) LDA (5 equiv), THF, –70 °C, 2 h; b) RX (**4**; 15 equiv), 6 h; c) aq NH_4Cl then wash. B: as for A, with HMPA (20 equiv) added to LDA. C: oxalic acid, THF–H_2O (1:1), reflux, 18 h.
[b] Determined by GC-MS (see ref. 24 for details).
[c] Complex mixture obtained.

electrophile induces specific monoalkylation, in contrast with the solution-state behaviour of aminonitriles in which an excess of reagents induces significant double alkylation. Sequential dialkylation of aminonitrile resins is thus facilitated, and these dialkylated materials have stability advantages over their small molecule equivalents. Two complementary cleavage protocols are available, with the choice depending on the sensitivity of the grafted functionality. The presence of HMPA cosolvent, sometimes a requirement for efficient solution state reactions, does not seem to be so important on the solid support (at least for monoalkylation), which is advantageous from an environmental point of view. These observations suggest a potential use for solid-supported aminonitrile chemistry, with possible advantages over the solution-state equivalent.

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(20) **Preparation of Resin 2**
Under argon, chloroacetonitrile (0.052 mL, 0.82 mmol) and Et_3N (0.115 mL, 0.82 mmol) were added to amine resin **1** (0.097 g, 0.062 mmol) pre-swollen in anhyd DMF (1 mL). The mixture was heated at 90 °C for 4 d. The resin was recovered by filtration then washed successively with DMF (20 mL), a mixture of DMF–H_2O (1:1, 20 mL), CH_2Cl_2 (20 mL), MeOH (20 mL), CH_2Cl_2 (20 mL), and MeOH (20 mL). The resin was finally dried over P_2O_5 under reduced pressure. HR-MAS ^1H NMR (300 MHz, $CDCl_3$): δ = 3.4–3.6 (H2), 3.9–4.1 (H4 and H3). HR-MAS ^{13}C NMR (75 MHz, $CDCl_3$): δ = 41 (C2), 58 (C3 and C4), 115 (C1). Combustion analysis N: 1.58% (1.13 mmol g^{-1}).
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(23) **General Alkylation**
Under an atmosphere of argon, a solution of LDA [prepared from 1.6 M BuLi in hexane (5 equiv) and DIPA (5 equiv)] and optionally HMPA (20 equiv) in THF (4 mL) at –70 °C was added dropwise by cannula to a carefully stirred suspension of supported aminonitrile **2** or **5a** (0.3 mmol) pre-swollen in anhyd THF (4 mL) and cooled to –70 °C. After 2 h, electrophile **4** (15 equiv) was added dropwise, and the mixture was stirred at –70 °C for a further 6 h. Saturated NH_4Cl solution (10 mL) was then added, and the mixture was allowed to warm to r.t. The resin was recovered by filtration and washed successively with H_2O (50 mL), a mixture of THF–H_2O (1:1, 50 mL), CH_2Cl_2 (50 mL), and MeOH (50 mL). The resin was finally dried under reduced pressure over P_2O_5 overnight.
(24) **Oxalic Acid Hydrolysis**
Aminonitrile resin **5** or **10** (0.3 mmol) was swollen in THF (15 mL) at r.t., then a solution of 30% aq oxalic acid (15 mL) was added. The mixture was heated at reflux overnight, then cooled to r.t., then a mixture of ice–H_2O was added. The resin was removed by filtration and washed with H_2O and $CHCl_3$. Liquid phases (filtrate and washings) were separated, and the aqueous phase was extracted once with $CHCl_3$. Combined organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure to give the carbonyl compound **6** or **7**. Product purity and identity (comparison with reference samples) was assessed by GC-MS.
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(27) **Copper Sulfate Methanolysis Procedure**
Aminonitrile resin **5** (0.2 mmol) was swollen in a few drops of DMF at r.t., then a solution of $CuSO_4 \cdot 5H_2O$ (2 equiv) in anhyd MeOH (4 mL) was added. The mixture was heated at reflux overnight, then cooled to r.t. The resin was removed by filtration and washed with pentane and CH_2Cl_2. Combined filtrate and washings were dried over $MgSO_4$, and evaporated under reduced pressure to give the dimethyl acetal **8**. The reaction product was analyzed by GC-MS. Product purity and identity (comparison with reference samples) was assessed by GC-MS.