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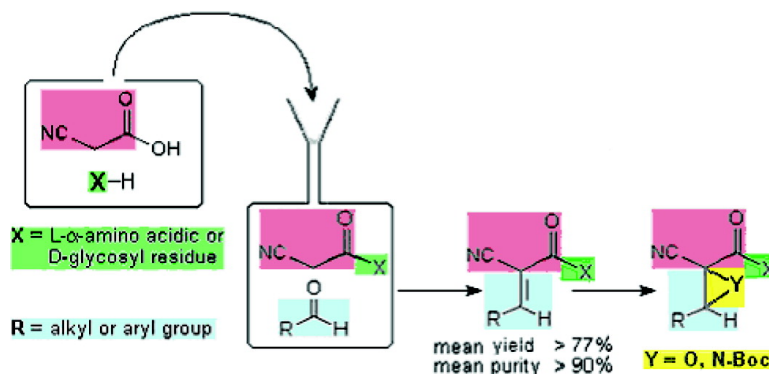
Parallel Solution-Phase Synthesis of Acrylonitrile Scaffolds Carrying l-α-Amino Acidic or d-Glycosyl Residues

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Parallel Solution-Phase Synthesis of Acrylonitrile Scaffolds Carrying L-α-Amino Acidic or D-Glycosyl Residues

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A practical and straightforward protocol for the preparation of a solution-phase library of acrylonitrile scaffolds is reported. Target compounds were obtained in high yield, stereoselectivity, and purity by two simple and practical steps from cyanoacetic acid. Moreover, our study proposes a synthetic approach starting from the constructed library to obtain three-membered heterocycles.

Introduction

Advances in parallel synthesis and combinatorial chemistry have provided discovery organizations with a powerful set of methods for the preparation of libraries of small organic molecules which are essential building blocks for the construction of more complex structures. Most usual organic synthetic methods aim to produce a single compound per well, and one of the topics of current combinatorial chemistry is to design small molecule libraries that are useful templates.[1,2]

Olefins are among the most attractive starting materials available to the synthetic chemist: they occasionally display biochemically and pharmacologically interesting properties. Their chemistry provides for the creation of diverse scaffolds and the attachment and display of various functionalities through the oxidative addition of heteroatoms to specifically placed olefinic sites. For example their importance is enhanced by their role as progenitors of still higher-energy intermediates such as epoxides, aziridines, or thiiranes, which are all suitable for a click chemistry[3] approach.

Recently, we studied the synthesis of electron-poor alkenes bearing a cyano group and their reactivity in amination reactions.[4] We focused on this function for its versatility, which stems from its extremely high polar-inductive effect, its excellent hydrogen-bond acceptor properties, and its minimal steric demand, often resulting in high-stereoselective preferences.[5] Furthermore, from a synthetic point of view, the cyano group represents a unique chameleonic moiety for its well-known feasibility of being converted into an array of different functional groups like acids, amides, and amines.[5a]

Results and Discussion

As part of our ongoing studies, here we propose a concise synthetic approach to the library construct of acrylonitrile derivatives from L-α-amino esters, amenable to semi-automated parallel solution-phase synthesis (Scheme 1).

Cyanoacetic acid **1** was made to react with L-α-amino esters in the presence of stoichiometric amounts of DCC and DMAP. After 1 h at room-temperature, HPLC analyses of the crude mixtures showed quantitative conversion of the starting materials. After fast filtration, methylene active compounds $2X_1-X_4$ were obtained in high yield and purity (>90% determined by HPLC). The successive Knoevenagel condensation reactions were performed according to literature procedures[6] that we have already used,[4] namely, by immediate addition of Al_2O_3 and the opportune aldehyde to cyanoacetamides $2X_1-X_4$. The overall yields of the resulting olefins, **3**, are reported in Table 1. As reported in the literature,[6,7] the stereochemistry of **3** was always E because of the minimal steric hindrance of the cyano group.

Alkylidene (entries 1−6, 8−11, 14, and 15) and arylidene cyanoacetamide derivatives (entries 7, 12, 13, 16, and 17), **3**, could be regarded as interesting compounds in pharmacological and medicinal fields. In fact, it is well-known that analogous compounds are effective protein tyrosine kinase (PTK) inhibitors, termed tyrphostins.[8] Their structural motif is an alkene with a cis-oriented nitrile and usually oxygenated benzene groups on the double bond.[9] In the past decade, the synthesis of this class of small molecules has attracted a lot of attention[10] because of their therapeutic applications demonstrated by the pioneering works of Levitzki and co-workers.[11]

Our solution-phase synthesis allows us to produce similar compounds in a large scale, with good yields (mean yield of >77%) and purities (mean purity of >90% by HPLC analyses and ¹H NMR spectra), in only two steps. Moreover,

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Scheme 1. Solution-Phase Synthesis of Acrylonitriles Carrying L-α-Amino Ester Residues
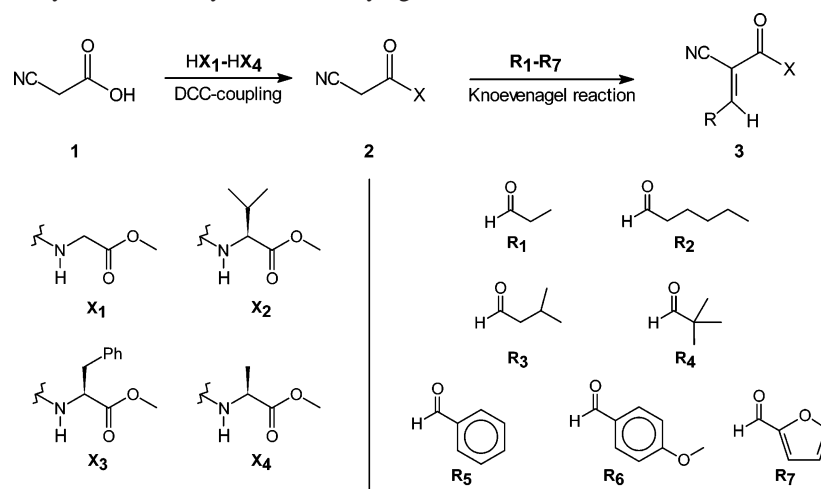
Table 1. Library of Acrylonitriles Carrying L-α-Amino Ester Residues

entry	compound 3	L-α-amino ester	R	yield (%)
1	X_1R_1	Gly-OMe	Et	62
2	X_1R_2	Gly-OMe	pentyl	68
3	X_1R_3	Gly-OMe	*i*-Bu	86
4	X_2R_1	Val-OMe	Et	71
5	X_2R_2	Val-OMe	pentyl	68
6	X_2R_3	Val-OMe	*i*-Bu	88
7	X_2R_7	Val-OMe	2-furyl	82
8	X_3R_1	Phe-OMe	Et	73
9	X_3R_2	Phe-OMe	pentyl	76
10	X_3R_3	Phe-OMe	*i*-Bu	92
11	X_3R_4	Phe-OMe	*t*-Bu	85
12	X_3R_6	Phe-OMe	$p\text{-}CH_3O\text{-}C_6H_4$	90
13	X_3R_7	Phe-OMe	2-furyl	82
14	X_4R_1	Ala-OMe	Et	78
15	X_4R_2	Ala-OMe	pentyl	83
16	X_4R_5	Ala-OMe	Ph	59
17	X_4R_6	Ala-OMe	$p\text{-}CH_3O\text{-}C_6H_4$	75

the introduction of an L-α-amino acid residue should leave unchanged the possibility of these molecules assuming the docking conformation, considered to be among the important factors of inhibition activity of tyrphostins.[12]

Encouraged by our results, we decided to attempt the same procedure to synthesize alkylidene and arylidene cyanoacetates bearing a D-glycosyl residue on the carboxylic function.

In particular, we selected, as natural compounds, a commercial pyranose residue carrying a primary free hydroxyl function and a furanose residue carrying a secondary free hydroxyl function (Scheme 2).

Application of the above-described protocol was very efficient when sugar with a primary free hydroxyl function was used as substrate affording the target olefins, **5**, as pure *E* isomers, in 1 h and in good overall yields (Scheme 2). On the other hand, when sugar with a secondary free hydroxyl function was reacted with **1** the reaction was sluggish, and after 16 h, only 70% conversion of the starting material was observed. The subsequent Knoevenagel condensation afforded the desired cyano acrylates, albeit in moderate overall yields. The minor efficiency level of the coupling reaction may be attributed to the increased steric hindrance of furanose residue carrying a secondary hydroxyl group.

Combinatorial libraries obtained starting from natural compounds seem to represent a valuable source of exploratory chemistry for novel drug discovery and development. Therefore, it is also possible to consider the cyano olefin derivatives **3** and **5** as suitable substrates for click chemistry[3] transformations and, with further research, to obtain different libraries from the same library. In particular, we focused our attention toward the synthesis of strained heterocycles, such as epoxides and aziridines. The first examples are reported in Scheme 3.
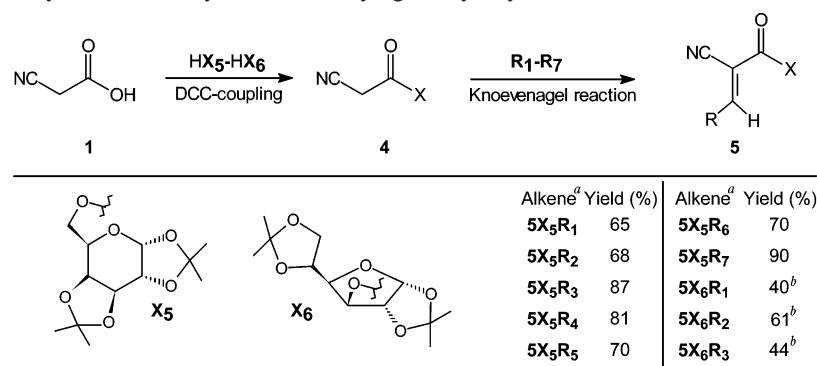
Epoxidation was obtained with *m*-chloroperoxybenzoic acid (*m*-CPBA) and K_2CO_3 in CH_2Cl_2.[13] With the use of *tert*-butyl nosyloxycarbamate (NsONH-Boc, Ns = 4-nitrophenylsulfonyl) in the presence of calcium oxide, the aziridination reactions were also successful via an aza-MIRC (Michael-initiated ring closure) reaction.[4] The small heterocycles were obtained in good yields, as separable diastereoisomers.[14] The selective removal of the Boc protecting group is an important step for the generation of a new site for further molecular growth: a first attempt performed on $7X_3R_3$, using a TBAF/THF procedure,[15] allowed us to obtain free aziridine in good yields.

Conclusions

We have developed a practical and straightforward parallel solution-phase synthesis of acrylonitrile derivatives bearing a natural chiral residue on the carboxylic function. Our protocol, requiring only two steps, demonstrates a wide applicability both for obtaining alkyl and aryl substituted acrylonitriles and for establishing fast and inexpensive purification methodologies. The yields are always coupled to a high purity of target products. Finally, we improved the potentiality of the constructed library by efficient methods to obtain an enhancement of both the size and the diversity of small molecule libraries.

Experimental Section

Materials and General Methods. All of the solvents and reagents were obtained commercially and were used as received. The IR spectra were recorded using $CHCl_3$ as the solvent. The ^{1}H NMR and ^{13}C NMR spectra were recorded by a spectrometer at 300 or 200 MHz and 75 or 50 MHz,

Scheme 2. Solution-Phase Synthesis of Acrylonitriles Carrying D-Glycosyl Residues

Alkene[a]	Yield (%)	Alkene[a]	Yield (%)
$5X_5R_1$	65	$5X_5R_6$	70
$5X_5R_2$	68	$5X_5R_7$	90
$5X_5R_3$	87	$5X_6R_1$	40[b]
$5X_5R_4$	81	$5X_6R_2$	61[b]
$5X_5R_5$	70	$5X_6R_3$	44[b]

[a] For R_1−R_7, see Scheme 1. [b] After flash chromatography on silica gel (eluent hexane/ethyl acetate 2/1).

Scheme 3. Synthesis of Strained Heterocycles

6: Y = O, **7**: Y = N-Boc
Yield = 83−90%
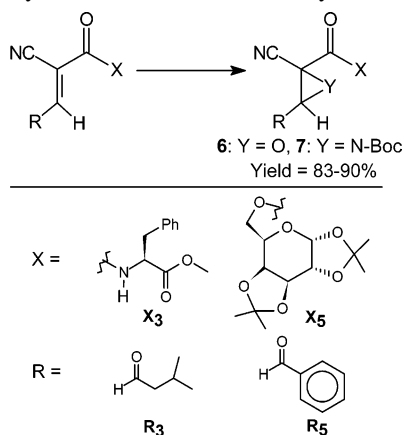
respectively, using CDCl$_3$ as the solvent and CHCl$_3$ as the internal standard. ESI MS analyses were performed using a quadrupole-time-of-flight (Q-TOF) mass spectrometer equipped with an ESI source and a syringe pump; the experiments were conducted in the positive-ion mode. HPLC analyses were performed with an instrument equipped with a differential refractometer, using an analytical column (3.9 × 300 mm, flow rate 1.3 mL/min). The eluent mixtures were hexane/ethyl acetate = 4/1 for the alkenes carrying the amino ester residues and hexane/ethyl acetate = 3/1 for analogous alkenes carrying the carbohydrate residues. Eluents were HPLC grade. The reaction steps were performed in parallel using a Carousel Reaction Station.

General Procedure for Parallel DCC Coupling Reaction. Four millimoles of HX$_1$−X$_6$ and a stoichiometric (catalytic for HX$_5$ and HX$_6$) amount of DMAP were added to a stirred solution of 4.0 mmol of **1** in 20 mL of CH$_2$Cl$_2$. After 15 min, 4 mmol of DCC was added batchwise to the mixture, and the reaction was allowed to stir for 1 h (16 h for HX$_6$) at room temperature. The solid residues were filtered off, and the organic layer was concentrated in vacuo and analyzed by HPLC. The crude methylene active product was used directly in the successive step without any further purification.

General Procedure for the Parallel Knoevenagel Condensation Reaction. A 3-fold molar excess of aldehyde and 3.0 g of basic Al$_2$O$_3$ (70−230 mesh ASTM) were added to a stirred solution of 2.0 mmol of **2** or **4** in 10 mL of CH$_2$-Cl$_2$. When the reaction was complete (TLC), the crude

product was filtered through a short plug filled with silica gel using a 2/1 hexane/ethyl acetate mixture. After evaporation of the solvents, the target olefin was obtained as pale yellow oil.

N-[(2*E*)-2-Cyano-5-methylhex-2-enoyl]-L-phenyl-alanine Methyl Ester (3X$_3$R$_3$). Pale oil. IR: 3402, 2247, 1744, 1683, 1619 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 0.92−1.04 (m, 6H), 1.79−1.95 (m, 1H), 2.36−2.45 (m, 2H), 3.09−3.24 (m, 2H), 3.73 (s, 3H), 4.82−4.96 (m, 1H), 6.55 (br, 1H), 7.06−7.18 (m, 2H), 7.20−7.38 (m, 3H), 7.64 (t, *J* = 8.1 Hz, 1H). ^{13}C NMR (CDCl$_3$): δ 22.2, 28.0, 37.6, 40.6, 52.4, 53.8, 110.7, 114.5, 127.3, 128.7, 129.0, 135.1, 158.9, 160.6, 171.0. HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for C$_{18}$H$_{22}$N$_2$NaO$_3$: 351.1685. Found: 351.1699.

(2,2,7,7-Tetramethyltetrahydro-3a*H*-bis^{1,3}dioxolo[4,5-b:4′,5′-d]pyran-5-yl)methyl (2*E*)-2-Cyano-3-phenylprope-noate (5X$_5$R$_5$). Pale oil. IR: 1728, 1607 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.32 (s, 3H), 1.34 (s, 3H), 1.45 (s, 3H), 1.53(s, 3H), 4.13−4.18 (m, 1H), 4.30−4.34 (m, 2H), 4.40 (dd, *J* = 5.4, 11.1 Hz, 1H), 4.47 (dd, *J* = 7.2, 11.1 Hz, 1H), 4.64 (dd, *J* = 2.4, 7.2 Hz, 1H), 5.52 (d, *J* = 2.4 Hz, 1H), 7.45−7.74 (m, 3H), 7.95−7.98 (m, 2H), 8.23 (s, 1H). ^{13}C NMR (CDCl$_3$): δ 24.4, 24.9, 25.9, 26.0, 65.0, 65.7, 70.4, 70.6, 70.7, 96.1, 102.7, 108.8, 109.6, 115.3, 129.2, 131.0, 131.3, 133.3, 155.2, 162.2. HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for C$_{22}$H$_{25}$NNaO$_7$: 438.1529. Found: 438.1521.

General Procedure for Epoxide Synthesis. A solution of unsaturated nitrile (**3** or **5**, 0.2 mmol) in CH$_2$Cl$_2$ was added to a mixture of *m*-CPBA (0.50 mmol) and K$_2$CO$_3$ (0.24 mmol) in CH$_2$Cl$_2$ at room temperature. After 3 h, the reaction mixture was washed with a NaHSO$_3$ solution (40%) and then with saturated aqueous NaHCO$_3$. The organic layer was dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. The epoxide was purified by flash column chromatography.

(2,2,7,7-Tetramethyltetrahydro-3a*H*-bis^{1,3}dioxolo[4,5-b:4′,5′-d]pyran-5-yl)methyl (2*R**,3*S**)-2-Cyano-3-phenylox-irane-2-carboxylate (6X$_5$R$_5$). Pale oil. IR: 2232, 1736 cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.16 (s, 6H), 1.27 (s, 3H), 1.34 (s, 3H), 3.90−3.96 (m, 1H), 4.06−4.10 (m, 1H), 4.12−4.18 (m, 1H), 4.28 (d, *J* = 6.6 Hz, 1H), 4.35(d, *J* = 6.6 Hz, 1H), 4.41−4.48 (m, 2H), 5.34−5.37 (m, 1H), 7.46 (s, 5H). ^{13}C NMR (CDCl$_3$): δ 23.3, 24.6, 25.2, 25.8, 41.0, 57.2, 65.3, 66.0, 70.5, 70.6, 70.7, 96.4, 103.1, 108.8, 110.1, 129.2, 131.1,

131.5, 133.6, 164.8. HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for $C_{22}H_{25}NNaO_8$: 454.1472. Found: 454.1490.

General Procedure for Aziridine Synthesis. Equimolar amounts of CaO and NsONHBoc were added to a stirred solution of unsaturated nitrile (**3** or **5**) in CH_2Cl_2. After the reaction was complete (TLC), the crude aziridines were filtered through plugs filled with silica gel using a 9/1 hexane/ethyl acetate mixture, and the products were obtained as pale yellow oils after solvent removal.

***N*-{[(2*R**,3*R**)-2-Cyano-3-isobutylaziridin-2-yl]carbonyl}-L-phenylalanine Methyl Ester (7X$_3$R$_3$).** Pale oil. IR: 3407, 2222, 1745, 1688, cm^{-1}. ^{1}H NMR (CDCl$_3$): δ 1.01 (d, *J* = 6.6 Hz, 6H), 1.45 (s, 3H), 1.52−1.64 (m, 2H), 1.80−1.98 (m, 1H), 3.02 (t, *J* = 6.6 Hz, 1H), 3.16 (d, *J* = 6.0 Hz, 2H), 3.74 (s, 3H), 4.81−4.87 (m, 1H), 6.91 (d, *J* = 7.2 Hz, 1H), 7.10−7.18 (m, 2H), 7.24−7.37 (m, 3H). ^{13}C NMR (CDCl$_3$): δ 21.9, 22.4, 26.7, 27.8, 37.7, 37.9, 39.5, 48.6, 52.6, 54.1, 83.5, 114.4, 127.6, 128.9, 129.2, 134.9, 155.9, 160.5, 170.5. HR-MS (ES Q-TOF) (*m/z*) [M + Na]$^+$ calcd for $C_{23}H_{31}N_3NaO_5$: 452.2156. Found: 452.2134.

Supporting Information Available. ^{1}H NMR spectra and HR-MS data are reported for all **3** and **5** compounds, for epoxide **6X$_5$R$_5$** and for aziridine **7X$_3$R$_3$**. This material is available free of charge via the Internet at http://pubs.acs.org.

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