Pergamon

Tetrahedron Letters 42 (2001) 2269–2271

TETRAHEDRON LETTERS

Universal Rink–isonitrile resin: application for the traceless synthesis of 3-acylamino imidazo[1,2-*a*]pyridines

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Received 27 November 2000; revised 19 January 2001; accepted 22 January 2001

Abstract—Rink resin was converted to isonitrile resin after formylation with HCO_2H/diisopropylcarbodiimide followed by $POCl_3$/diisopropylethylamine dehydration. This polymer-supported isonitrile was then employed in the multi-component synthesis of imidazo[1,2-*a*]pyridines. The resin-bound imidazo[1,2-*a*]pyridine was acylated and spontaneously released by acyl chloride treatment in dichloroethane. © 2001 Elsevier Science Ltd. All rights reserved.

Isonitrile involved multi-component reactions (MCRs) are atom-economic methods of installing molecular diversity.[1] The extensive applications of these reactions, however, are restricted by the malodor and the limited availability of isonitriles. One enticing remedy to these problems is universal isonitriles and their solid-support versions,[2] depicted in Fig. 1. These reagents have been used in the classical MCRs, such as Ugi and Passerini reactions, where an isonitrile furnishes an amide moiety in the final product. The alkyl groups of this class are deliberately crafted for easy activation and dissociation of the amide during the post-MCR modification. Recent advances in MCR have led to the discovery of several novel reactions;[3] e.g., the formation of imidazo[1,2-*a*]pyridine via the condensation of 2-aminopyridine, aldehyde and isonitrile.[3c] Instead of becoming an amide, the isonitrile in these MCRs transforms into an enamine after the reaction.

We envisaged that a polymer-supported universal isonitrile for the non-classical MCR would enable on-resin elaboration and traceless cleavage at the enamine site. An acid-labile linker is therefore essential for the selective release of the product. After careful evaluation of the commercially available solid supports, we chose Rink resin as the platform of this endeavor.

Isonitrile functionality was installed on the Rink resin in two simple steps. As illustrated in Scheme 1, formylation with HCO_2H/diisopropylcarbodiimide (DIC) fol-

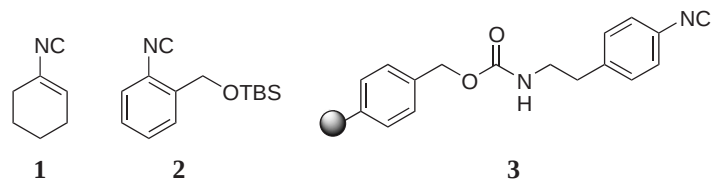
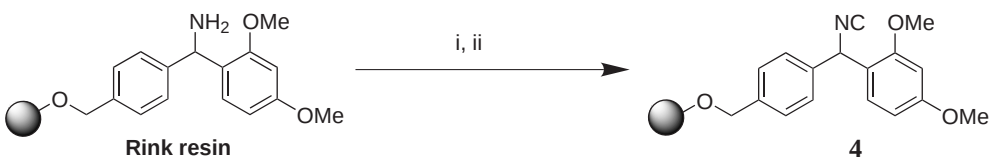


Figure 1. Various universal isonitriles.



Scheme 1. (i) DIC/HCO_2H/pyridine, CH_2Cl_2; (ii) $POCl_3$/DIPEA, 0°C to rt, 6 h.

Keywords: combinatorial synthesis; solid-phase synthesis; heterocyclic chemistry; multi-component reaction.

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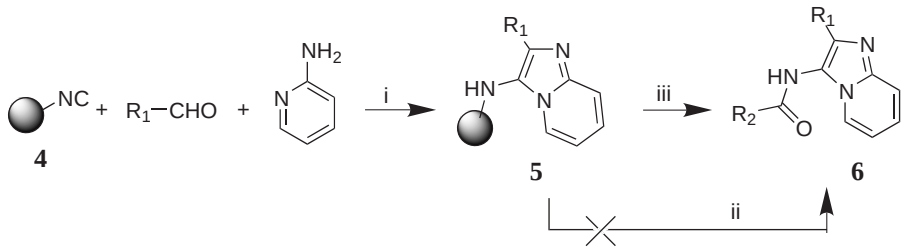
PII: S0040-4039(01)00159-9

lowed by $POCl_3$/diisopropylethylamine (DIPEA) dehydration afforded resin-bound isonitrile **4**. The resin is odor free and stable under refrigeration over a period of 12 months. The process was scaled up to 50 grams and still provided product of excellent quality.

The application of this resin was examined in the MCR preparation of imidazo[1,2-*a*]pyridine (Scheme 2). The isonitrile resin **4**, 2-aminopyridine, an aldehyde and a catalytic amount of toluenesulfonic acid (TsOH) were agitated in $CHCl_3$/MeOH/trimethylorthoformate (TMOF) to furnish the resin-bound imidazo[1,2-*a*]pyridine **5**. Elaboration on the enamine of intermediate **5** via base-mediated acylation or sulfonylation proved to be very difficult, even at drastic conditions. However, acylation and spontaneous cleavage was effectively achieved by heating the resin with acyl chlorides solely in dichloroethane (DCE).[4] The reaction was usually complete after overnight heating with the acylated product **6** being the only cleavage product. When R_1 was an aromatic (Table 1, entries e–g), prolonged reaction was necessary. The attenuated nucleophilicity of the enamine evidently slowed down the acylative cleavage in the latter case. In this study, resin capture is a very effective clean-up method. The products were extracted from the cleavage mixture by DOWEX™ ion-exchange resin and then released as free bases by 10% DIPEA/MeOH. Further purification using flash column chromatography or HPLC afforded analytically pure products.

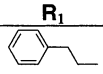
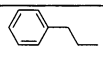
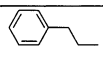
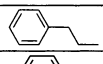
In conclusion, we have developed a feasible method for preparing Rink–isonitrile resin. In synergy with acylative cleavage, this polymer-bound universal isonitrile has provided easy access to 3-acylamino imidazo[1,2-*a*]pyridines via the MCR avenue. More studies are ongoing to scrutinize the cleavage mechanism. The application of this novel solid support in other MCRs is also under investigation. The results of these studies will be reported in due course.

General preparation method for Rink–isonitrile resin 4: Rink resin was deprotected and suspended in CH_2Cl_2. Under ice cooling, pyridine (1 equiv.) and HCO_2H (5 equiv.) were added, followed by DIC (5 equiv.). The suspension was stirred for 1 h at 0°C and then at ambient temperature until the coupling was complete (usually 3 h, as judged by Kaiser test[5]). The resin was washed with DMF, MeOH, CH_2Cl_2 and dried for the next step.



Scheme 2. (i) MeOH/$CHCl_3$/TMOF, TsOH (1 equiv.), overnight; (ii) a variety of base-mediated acylation methods; (iii) R_2COCl (8 equiv.), DCE, 50°C, 16 h.

Table 1. 3-Acylamino imidazo[1,2-*a*]pyridines prepared via Scheme 2

Entry	R_1	R_2	6 [%][a]	Reaction time	Yield %
a			94.9	16 h	30.8
b			92.1	16 h	33.7
c			87.1	16 h	23.4
d			88.5	16 h	30.4
e			90	48 h	58.0[b]
f			100	48 h	60.3[b]
g			86.0	48 h	64.1

a. Content in the crude product after the resin cleanup, judged by LC-MS at 220 nm. b. The crude yield after the resin cleanup.

The formylated Rink resin was suspended in anhydrous CH_2Cl_2. Under ice cooling and Ar protection, DIPEA (15 equiv.) was cannulated. $POCl_3$ (5 equiv.) was then added slowly. The suspension was stirred for 5 h at 0°C, followed by further stirring for 1 h at ambient temperature. The resin was then washed with CH_2Cl_2 and ether, and dried in vacuum to a constant weight. The disappearance of formyl CO ($\sim$1740 cm^{-1}) and the emergence of NC ($\sim$2150 cm^{-1}) absorption in the IR spectrum is the most obvious evidence of the conversion.

MCR on the Rink–isonitrile resin (Table 1, entry a): Hydrocinnamaldehyde (3.08 ml, 14.4 mmol), 2-aminopyridine (1.36 g, 14.4 mmol) and TsOH (0.32 g, 1.8 mmol) were mixed in $CHCl_3$/MeOH/TMOF (1/1/1, v/v/v) for 2 h. The mixture was then added to the isonitrile resin **4** (2.0 g, 1.8 mmol). The suspension was agitated overnight at ambient temperature. The resin was washed with *N*,*N*-dimethylformamide (DMF), MeOH, 10% DIPEA/CH_2Cl_2, CH_2Cl_2, MeOH, and then dried to afford the intermediate resin **5a**.

Traceless cleavage with acyl chloride: Resin **5a** (0.2 g, 0.18 mmol) was suspended in DCE. Benzoyl chloride (0.17 ml, 0.96 mmol) was added. The suspension was agitated for 5 h at room temperature, then for 16 h at 50°C. The cleavage filtrate was collected and evaporated to dryness. The oily residue was dissolved in methanol and added to DOWEX4-500 ion-exchange resin (1 g). The suspension was agitated for 5 h. The resin was filtered and washed with DMF, MeOH, CH_2Cl_2, and MeOH. The crude product was released from the resin by eluting the resin with a 10% DIPEA/MeOH solution. The methanolic solution was evaporated and the crude product was purified by HPLC to afford **6a**.[6] Yield 24.3 mg, 30.8% after five steps from Rink amide resin.

Acknowledgements

The authors are grateful to Dr. Dave Portlock and Professor Henry Rappaport for their helpful comments during the course of this work.

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6. Spectral data for **6a**: ^{1}H NMR (300 MHz, CD_3OD, δ): 8.53 (dt, $J_1=1.1$ Hz, $J_2=2.0$ Hz, $J_3=6.8$ Hz, 1H), 8.10 (m, 1H), 8.019 (m, 1H), 7.93 (m, 1H), 7.73 (m, 1H), 7.63 (m, 1H), 7.53 (m, 1H), 7.29–7.19 (m, 4H), 3.24 (m, 2H), 3.11 (m, 2H). $^{13}C\{^1H\}$ (150 MHz, CD_3OD, δ): 26.1, 33.9, 111.8, 117.2, 118.6, 125.7, 126.5, 128.1, 128.2, 128.6, 128.8, 132.1, 133.1, 133.7, 138.0, 140.0, 168.7. MS (DCI): m/z 342 $[M+H]^+$.
6c: ^{1}H NMR (300 MHz, CD_3OD, δ): 8.52 (d, $J=6.96$ Hz, 1H), 8.04–7.98 (m, 1H), 7.93 (m, 1H), 7.90 (m, 1H), 7.52 (m, 1H), 7.43 (m, 1H), 7.23 (m, 5H), 6.77 (q, $J_1=1.83$ Hz, $J_2=3.66$ Hz, $J_3=5.49$ Hz, 1H), 3.21 (m, 2H), 3.09 (m, 2H). $^{13}C\{^1H\}$ (150 MHz, CD_3OD, δ): 26.1, 33.8, 111.9, 112.6, 117.2, 117.3, 125.7, 126.5, 128.2, 128.6, 133.7, 139.8, 146.8, 158.9. MS (DCI): m/z 332 $[M+H]^+$.
6g: ^{1}H NMR (300 MHz, CD_3OD, δ): 8.45 (dt, $J_1=1.1$ Hz, $J_2=7.7$ Hz, $J_3=8.8$ Hz, 1H), 8.00 (m, 1H), 7.92 (m, 1H), 7.81 (m, 2H), 7.60 (m, 3H), 7.52 (m, 1H), 2.02 (m, 1H), 1.06 (m, 4H). $^{13}C\{^1H\}$ (150 MHz, CD_3OD, δ): 8.1, 13.7, 112.4, 117.2, 125.4, 127.5, 129.4, 130.6, 133.7, 138.8, 176.7. MS (DCI): m/z 278 $[M+H]^+$.