Multi-Component Synthesis of Imidazo[1,2-*a*] Annulated Heterocycles on α-Isocyano Resin Esters

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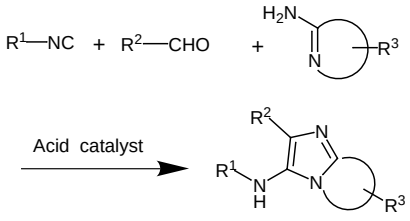
Abstract: The multi-component synthesis of imidazo[1,2-*a*] annulated heterocycles was performed on the α-isocyano resin esters. This solid phase approach addresses the limited availability issue of isonitrile reagents without compromising the overall diversity of the chemistry.

Key words: multi-component condensation, isonitrile resin, combinatorial synthesis, amino acid, 3-amino imidazole

Acceleration of drug discovery has generated growing demands for expeditious methods to produce therapeutic candidates. Isonitrile-based multi-component condensation (MCC) therefore has emerged as a simple and resource efficient approach to a large number of discrete structures.[1] In practice, these reactions are often performed on a solid support that tethers one of the reaction components such as amine, aldehyde or isonitrile. Immobilization of an isonitrile on a solid support is particularly intriguing due to the relief of the reagent's notorious malodor.[2] In order to create a polymer-bound isonitrile source with broad structural diversity, we recently developed a practical method to prepare α-isocyano resin esters from commercially available α-amino acid resins.[3]

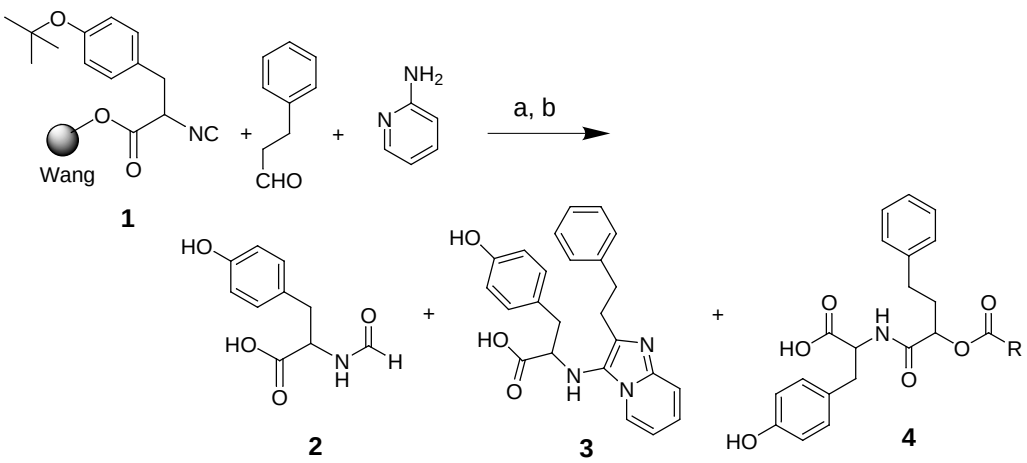


Scheme 1

This communication reports a novel application of the α-isocyano resin esters in the MCC synthesis of imidazole[1,2-*a*] annulated heterocycles. Imidazo[1,2-*a*] annulated heterocycles have been widely used as cerebraprotective agents,[4a] antimicrobials,[4b] cardiac stimulating agents,[4c] gastric acid secretion inhibitors[4d] and anti-inflammatory agents.[4e] Recently these molecules were constructed by a new MCC reaction involving an isonitrile, an aldehyde and a cyclic amidine (Scheme 1).[5] The reaction has been shown amenable to the attachment of any of the three reactants to a solid support.[5a] In spite of the simplicity and convenience of this new method, the diversity of the chemistry is limited by the commercial availability of the isonitriles.[6] One approach to address this issue is to perform the MCC on a polymer-supported 4-formyl benzoate using 1,1,3,3-tetramethybutyl isonitrile.[6] This isonitrile permits post-MCC dealkylation to furnish a primary amine for further structural elaboration. Whereas this approach circumvents the limitation of isonitrile reagents, it abandons the diversity advantage of commercially available aldehydes and the atom efficiency of the MCC reaction. We suggest that adoption of a new class of isonitrile resources such as α-isocyano resin esters would be a more convenient and straightforward solution. Considering the commercial availability of amino acid resins, this approach will dramatically enlarge the diversity scope of the chemistry.

The reaction in Scheme 2 was employed to optimize the acid catalyst. Scandium triflate ($Sc(OTf)_3$),[5a] acetic acid (HOAc)[5c] and perchloric acid ($HClO_4$)[5d] have been used to mediate the MCC. $Sc(OTf)_3$ was not adapted because of the concerns on its cost and moisture sensitivity in high throughput library production. Our experiments suggested that carboxylic acids (RCO_2H), such as HOAc and benzoic acid, trigger a Passerini side reaction[7] to yield the impurity **4** (Table 1). Mineral acids such as $HClO_4$, even at a trace quantity, results in hydrolysis of polymer-bound isonitrile to yield formamide **2**. *p*-Toluenesulfonic acid (TsOH), as an alternative, is so far the only acid that induces the MCC without these side effects.[8]

A series of bicyclic heterocycles as shown in Table 2 were prepared using various isocyano resin esters.[9-11] The MCC performed well with both aliphatic and aromatic aldehydes, and most of the synthesis afforded products in good purity and isolated yield. The stereochemical integrity of the chemistry was investigated. The α-isocyano resin esters derived from D- and L-Tyr(OtBu) Wang resins were used to prepare the two respective enantiomers of **3**. The isolated products were analyzed by standard C18 and chiral column HPLC.[12] The results of this study implicated that the MCC on both resins afforded the same racemic mixture. The racemization was presumably introduced during the resin preparation. We are addressing this issue by preparing enatiomerically pure isocyano resin esters. The results will be reported in due course.



Scheme 2 a) $CHCl_3$/TMOF/MeOH, 1/1/1 and an acid catalyst. b) 20% TFA/CH_2Cl_2, 2 × 30 min.

Table 1 Studies on acid catalyst selection[a]

Acid	Amount (eq to resin)	Amine/ acid	**2** %[b]	**3** %[b]	**4** %[b]
AcOH	2	4/1	18.5	74.0	6.0
	4	2/1	17.5	76.5	7.6
	6	4/3	21.0	72.7	5.7
	8	1/1	32.4	58.5	7.1
	12	2/3	8.1	82.7	8.3
Benzoic acid	4	2/1	2.5	81.2	14.8
$HClO_4$	0.1	80/1	40.4	54.8	0
TsOH	1	8/1	0	93.3	0
	2	4/1	0	95.7	0
	4	2/1	0	94.4	0
	6	4/3	0	94.2	0
	8	1/1	0	95.3	0

a) See the typical experimental procedure for the reaction conditions. b) Measured by HPLC, conditions: *Waters symmetry C18, 150* × 3.9 mm (5μm); 25-min linear gradient elution from 95%A:5%B to 95%B (A: water with 0.1% CF_3CO_2H; B:acetonitrile with 0.1% CF_3CO_2H); flow: 1.0 ml/min; λ = 210 nm.

Acknowledgement

The author thanks Mr. Thomas Burt and Ms. Anne Russell for their analytical support.

References and Notes

(1) For a recent review on multi-component reactions, see: Ugi, I.; Domling, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168-3210.

(2) There are several methods to prepare polymer-bound isonitriles. For a recent one, see: Kulkarni, B. A.; Ganesan, A. *Tetrahedron Lett.* **1999**, *40*, 5633-5636 and the references there in.

(3) We have found that the published protocols (ref. 2) do not provide efficient and clean isonitrile formation on α-amino acid resins. A practical method was therefore developed using Waki and Meienhofer's formylation (*J. Org. Chem.* **1977**, *42*, 2019) and Nunami's $POCl_3$/DIPEA dehydration (*Synthesis* **1990**, 781-782) procedures.
The typical procedure to prepare a α-isocyano resin ester: A commercial amino acid resin ester is deprotected and dried. The dry resin is suspended in CH_2Cl_2. Under ice cooling, pyridine (1 equiv) and HCO_2H (5 equiv) are added, followed by diisopropylcarbodiimide (5 equiv). The suspension is stirred 1h at 0 °C and then at ambient temperature till the reaction is complete (usually 3 h, judged by Ninhydrin test). The resin is washed and dried for the next step. The formylated amino acid resin is suspended in anhydrous CH_2Cl_2. Under ice cooling and Ar protection, diisopropylethylamine (DIPEA, 15 equiv) is cannulated. Then $POCl_3$ (5 equiv) is slowly added. The sus-pension is stirred for 5 h at 0 °C and 1 h at ambient tem-perature. The resin is then washed with CH_2Cl_2, ether, and dried in vacuum to a constant weight. The disappearance of formyl CO (~1740 cm^{-1}) and the emergence of NC (~2150 cm^{-1}) absorption in the IR spectrum is the most obvious evidence of the conversion.

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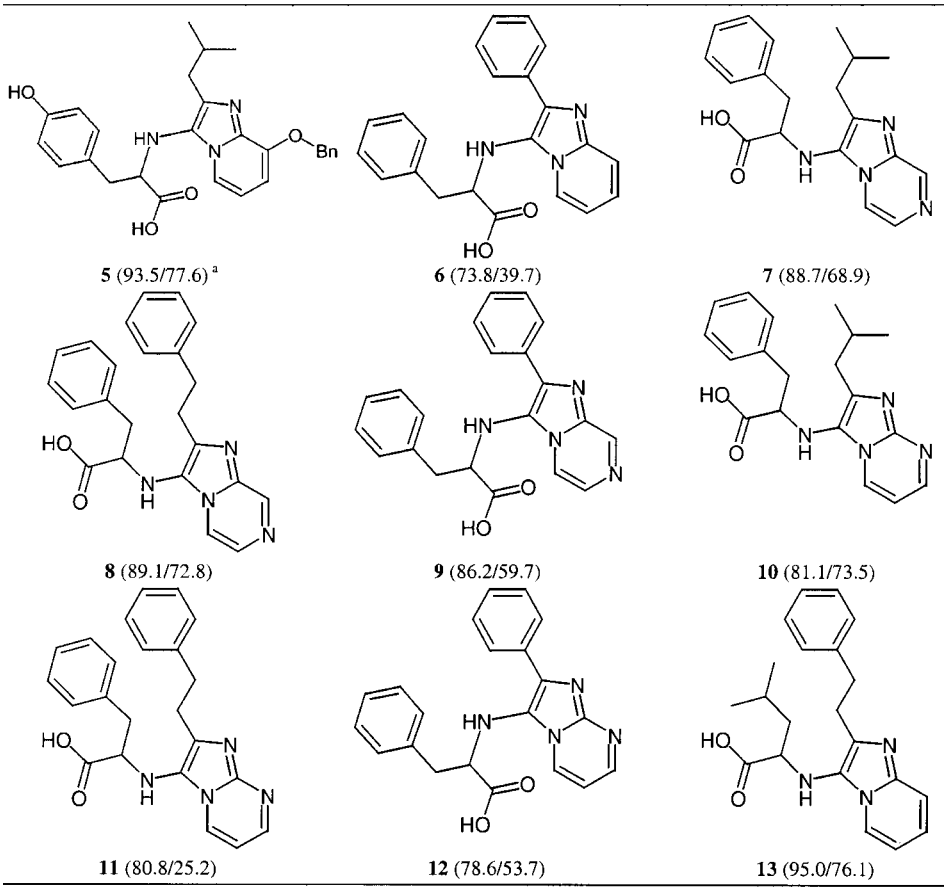
(7) For a recent review on Passerini reactions, see: Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123-131.

Table 2 Imidazo [1,2-*a*] annulated heterocycles prepared on α-isocyano resin esters



a) LC% (UV at 210 nm)/yield%

(8) **The experimental procedure for 3:** Hydrocinnamaldehyde (0.22 mL, 1.68 mmol), 2-aminopyridine (0.16 g, 1.68 mmol) and TsOH (0.04 g, 0.42 mmol) were mixed in $CHCl_3$-MeOH-trimethylorthoformate (1/1/1, v/v/v) for 1 h. The mixture was then added to the isonitrile resin **1** (0.3 g, 0.21 mmol, from Fmoc-Tyr(O^{t}Bu)-Wang resin). The suspension was agitated at ambient temperature overnight. The resin was washed with N,N-dimethylformamide (DMF), MeOH, 10% DIPEA/CH_2Cl_2, CH_2Cl_2 and MeOH, then dried. The product was released from the solid support by treating the resin with 20% TFA/CH_2Cl_2 (2 × 30 min) at room temperature. The cleavage filtrate was evaporated to dryness and the crude product was recrystallized from MeOH/ether to afford **3** as a white solid 27.6 mg, 32.8% in 4 steps from Fmoc-Tyr(OtBu) Wang resin.

(9) Spectral data for **3**: ^{1}H NMR (300 MHz, CD_3OD, δ) 7.82-7.686 (m, 3H), 7.29-7.15 (m, 8H), 6.80 (dt, J_1 = 2.0 Hz, J_2 = 8.61 Hz, 2H), 3.67 (dd, J_1 = 3.84 Hz, J_2 = 10.2 Hz, 1H), 3.20 (dd, J_1 = 3.9 Hz, J_2 = 13.7 Hz, 1H), 3.09 (m, 2H), 3.48 (m, 2H), 2.85 (dd, J_1 = 10.1 Hz, J_2 = 13.7 Hz, 1H). ^{13}C{^{1}H} (150MHz, CD_3OD, δ) 177.3, 158.1, 141.7, 138.2, 134.2, 132.3, 130.4, 130.1, 129.9, 129.2, 128.0, 126.8, 117.6, 116.8, 112.7, 64.5, 40.3, 36.1, 27.3. MS (DCI): m/z 402 $[M+H]^+$.

(10) Compound **9**: yielded 38.5 mg from 0.18 mmol resin (59.7%). ^{1}H NMR (300 MHz, CD_3OD, δ) 8.77 (s, 1H), 8.38 (d, J = 4.8 Hz, 1H), 7.78 (d, J = 4.2 Hz, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.74 (m, 1H), 7.35-7.26 (m, 8H), 3.94 (dd, J_1 = 4.4 Hz, J_2 = 9.5 Hz, 1H), 3.20 (dd, J_1 = 4.4 Hz, J_2 = 13.7 Hz, 1H), 3.01 (dd, J_1 = 9.5 Hz, J_2 = 13.6 Hz, 1H). ^{13}C{^{1}H} (150MHz, CD_3OD, δ) 177.1, 142.8, 139.2, 134.5, 131.0, 130.2, 129.8, 129.7, 129.1, 128.9, 128.2, 119.0, 62.4, 40.8. MS (DCI): m/z 359 $[M+H]^+$.

(11) Compound **11:** yielded 25.2 mg from 0.18 mmol resin (25.2%). ^{1}H NMR (300 MHz CD_3OD, δ) 8.74 (dd, J_1 = 1.8 Hz, J_2 = 4.39 Hz, 1H), 8.08(dd, J_1 = 1.8 Hz, J_2 = 6.8 Hz, 1H), 7.36-7.19(m, 11H), 3.72 (dd, J_1 = 3.9 Hz, J_2 = 10.1Hz, 1H), 3.30 (d, J = 4.0 Hz, 1H), 3.05-2.89 (m, 5H). ^{13}C{^{1}H} (150MHz, CD_3OD, δ) 177.3, 159.4, 156.5, 142.8, 141.9, 140.0, 135.#, 132.6, 131.3, 130.1, 130.0, 129.9, 128.5, 128.0, 127.5, 113.5, 64.6, 41.1, 36.1, 27.8. MS (DCI): m/z 387 $[M+H]^+$.

(12) The two products showed a single peak when they were co-injected on a C18 column, but two peaks on a chiral column with either co-injection or separated injections. The injection methods do not change the retention time of the peaks. The analytical conditions were as follows: *a) Waters symmetry C18, 150* × 3.9 mm (5μm); 20-min linear gradient elution from 80%A:20%B to 100%B (A: 95/5/0.1; B: 5/95/0.1, water/acetonitrile/formic acid, v/v/v); flow: 1.0 ml/min; λ = 283 nm. b)Keystone chiral/RSA, 50 × 4.6 mm (5μm); isocratic elution, 90%A:10%B (A: 25 mM phosphate buffer; B: acetonitrile); 1.0 ml/min; λ = 283 nm.

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