Pergamon

Tetrahedron Letters 39 (1998) 5469–5472

TETRAHEDRON LETTERS

A Three-Component Solid-Phase Synthesis of 3-Aminoimidazo[1,2-a]azines

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Received 29 April 1998; revised 19 May 1998; accepted 21 May 1998

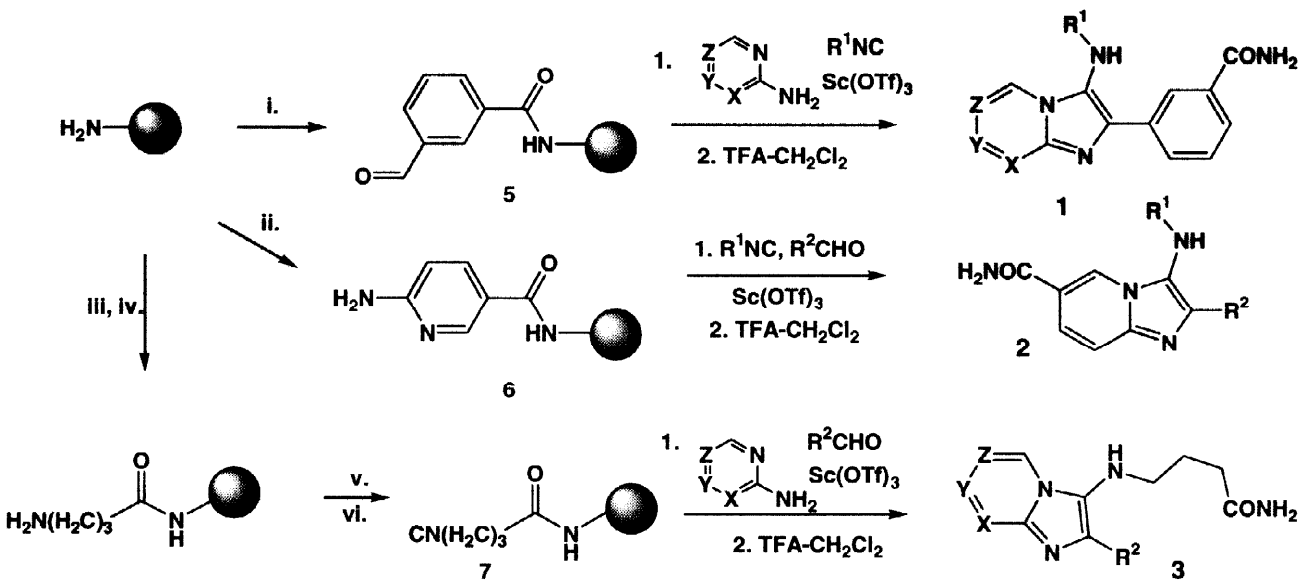
Abstract: The three-component condensation between a 2-aminoazine, an aldehyde and an isonitrile catalyzed by scandium triflate was conducted on a solid support with any of the three reacting functional groups tethered to Rink amide resin via an appropriate bifunctional carboxylic acid. The resulting resin-bound 3-aminoimidazo[1,2-a]azines could be efficiently acylated prior to cleavage.

Combinatorial methods of synthesis[1] have been developed to meet the challenge of producing large numbers of compounds for high-throughput screening. The parallel synthesis of large arrays of single compounds is now an important component of this process with multiple component condensations (MCCs)[2] being particularly attractive for rapid access to large numbers of structural analogs in a single step. There has thus been recent interest in the application of the Ugi,[2,3] Passerini,[2b] Biginelli,[4] and other[5] MCCs to the solid-phase thereby simplifying work up and enabling reactions to be driven to completion by using reagent excesses subsequently removed by filtration. Recently,[6] we reported a new three-component condensation (3CC) in which an imine formed from a 2-aminoazine and an aldehyde is attacked by an isonitrile to give a nitrilium ion that undergoes intramolecular cyclization affording 3-aminoimidazo[1,2-a]pyridines or pyrazines with previously unreported substitution patterns. Related heterocyclic systems have been well studied by medicinal chemists; thus, examples of cytoprotective,[7] cardiac stimulating,[8] anti-bacterial,[9] and anti-fungal[10] agents as well as bradykinin[11] and benzodiazepine receptor antagonists[12] have been reported. In order to extend this 3CC reaction to less reactive inputs and to enable subsequent reactions to be carried out without the need for isolation of intermediates, it was of interest to attempt representative transformations on the solid-phase.

A model compound, **1a,** (Table 1) was first prepared using solution phase conditions[6] by reaction of 3-formylbenzamide with 2-aminopyridine and benzylisonitrile in the presence of $Sc(OTf)_3$.[6,13] The purified and fully characterized[14] imidazo[1,2-a]pyridine derivative **1a** was used to construct a calibration curve of mass versus peak area in the reverse phase LC trace with the detector set at 254nm to enable both yields and purities to be assessed for small amounts of related compounds cleaved from resins.[15] A resin-bound aldehyde **5**, prepared by anchoring 3-carboxybenzaldehyde to Rink amide resin (RAM) in the presence of HATU, was converted to an imine by reaction[16] with 2-aminopyridine in CH_2Cl_2-MeOH (3:1) solution in the presence of $Sc(OTf)_3$ catalyst (Scheme 1) and allowed to react with benzylisonitrile. After 48h, TFA induced cleavage afforded the 3CC product **1a** in comparable yield to that obtained by the solution phase method as assessed by HPLC (Table 1). Aminopyrazine and 2-aminopyrimidine also afforded 3CC products **1b** and **1c**, respectively, (Table 1) in high purities but the expected 3CC product **1d** was not detected when 4-aminopyrimidine was used as the amine input (Table 1). A resin-bound 2-aminoazine, **6**, prepared by activating 6-aminonicotinic acid using HATU and coupling to RAM resin, was also found to undergo the 3CC reaction giving high purity products **2a-2c** after cleavage from the resin, albeit in lower yields compared with products obtained from the anchored aldehyde (Table 1).

0040-4039/98/$19.00
PII: S0040-4039(98)01113-7

Scheme 1.

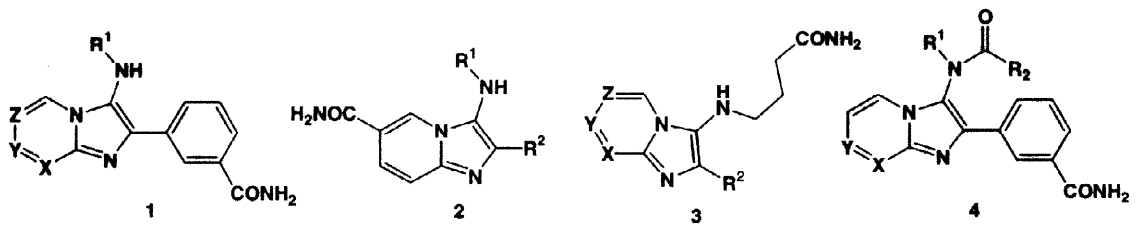


Reagents and conditions: i. 3-Carboxybenzaldehyde, HATU, DIEA. ii. 6-Aminonicotinic acid, HATU, DIEA. iii. Fmoc-GABA-OH, HATU, DIEA. iv. Piperidine-DMF (1:4). v. 2,3,5-trichlorophenylformate, DMF. vi. CCl_4, PPh_3, Et_3N, CH_2Cl_2.

The most attractive strategy for the solid-phase synthesis of these compounds is to anchor the least readily available component, namely the isonitrile, to the resin particularly as the 3CC then essentially involves resin-capture[17] of an imine which is readily generated in solution by a variety of methods. A resin isonitrile **7** for demonstration of this principle was prepared by anchoring Fmoc-GABA to RAM resin. After deprotection (piperidine-DMF), the anchored amine was formylated by treatment with 2,4,5-trichlorophenylformate.[18] Dehydration to the isonitrile was accomplished using PPh_3, CCl_4 and Et_3N as reported previously for a related formamide bound to a solid-support.[19] Imine formation between 2-aminopyridine and benzaldehyde at a concentration of 0.5 M in CH_2Cl_2-MeOH (3:1) in the presence of $Sc(OTf)_3$ was followed by addition of the resin-bound isonitrile. After 48h at ambient temperature, cleavage using TFA-CH_2Cl_2 afforded **3a** in low yield but reasonable purity. Use of other aromatic and aliphatic aldehydes in the 3CC reaction afforded compounds **3e-3g** in comparable yields and purities. 2-aminopyrazine and 2-aminopyrimidine proved to be reactive amine inputs affording compounds **3b** and **3c** respectively but the attempted condensation with 4-aminopyrimidine gave a complex mixture with the expected product, **3d,** present as a minor component only (Table 1).

3-Aminoimidazo[1,2-a]pyridines and pyrazines bound to the solid-support could be further functionalized by treatment with excess of an acid chloride. The resultant amides **4a** to **4d** were obtained in high yields and purities after TFA-CH_2Cl_2 induced cleavage. However, although the resin-bound pyrimidine analogs also underwent acylation reactions, the products **4e** and **4f** were obtained in much lower yields and purities (Table 1). Ureas were also prepared successfully on the solid-phase. For example, resin-bound **1b** reacted cleanly with 2,4-difluorophenylisocyanate in CH_2Cl_2 to give the corresponding urea in 80% yield and 95% purity after TFA induced cleavage.

Table 1. Solid Phase Three Component Condensations



Compd.	X	Y	Z	R^1	R^2	Yield[a] (%)	Purity[b]
1a	CH	CH	CH	CH_2Ph		65 69[c]	92 69,[c] (100)[d]
1b	CH	N	CH	CH_2Ph		78	98
1c	N	CH	CH	CH_2Ph		26	98
1d	CH	CH	N	CH_2Ph		0	0[e]
1e	CH	CH	CH	cyclohexyl		76	93
2a				CH_2Ph	Ph	30	90
2b				CH_2CH_2-3,4-$C_6H_3(OMe)_2$[f]	Ph	55	92
2c				cyclohexyl	cyclohexyl	80	82
3a	CH	CH	CH		Ph	30	85
3b	CH	N	CH		Ph	50	60
3c	N	CH	CH		Ph	50	70
3d	CH	CH	N		Ph	5	10
3e	CH	CH	CH		cyclohexyl	40	70
3f	CH	CH	CH		4-$MeOC_6H_4$	40	94
3g	CH	CH	CH		4-$CF_3C_6H_4$	50	98
4a	CH	CH			Ph	80	95
4b	CH	CH			2,4-diFC_6H_3	80	95
4c	CH	N			Ph	70	85
4d	CH	N			2,4-diFC_6H_3	65	80
4e	N	CH			Ph	20	40
4f	N	CH			2,4-diFC_6H_3	25	45

a. Overall yield for two steps (compounds 1 and 2), four steps (compounds 3), or one step (compounds 4). Yields were calculated from HPLC peak areas (see text) and are based on resin-loadings. b. Relative peak area with detector set at at 254 nm. c. solution phase synthesis.[6] d. After prep. tlc. e. 3-formylbenzamide recovered. f. note20

In conclusion, our recently reported[6] 3CC has been applied to the solid-phase (with any of the three reactants anchored to the support) affording moderate to good yields of high purity imidazo[1,2-a]azines for most amine inputs; a second step, wherein the amino group is functionalized, can also be effected prior to cleavage. These findings extend the application of our previous report[6] to new inputs and enable the production of libraries of these pharmacologically relevant heterocycles on automated solid-phase synthesizers. The extension of the 3CC reaction to resins that lead to products other than amides is in progress.

Acknowledgments: I am grateful to Drs. C. A. Burns and M. Minkoff for recording high resolution ESI-TOF mass spectra at PE Biosystems Contract R&D Center, Framingham, MA and to David Lok and Paul Fleming for technical assistance.

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14. (a) Compound **1a** was isolated in 69% yield by chromatography on silica gel eluting with CH_2Cl_2-MeOH. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.45 (1H, s), 8.15 (d, 1H, J= 7 Hz), 7.95 (1H, d, J= 9 Hz), 7.78 (1H, d, J = 9 Hz), 7.47 (2H, m), 7.30 (5H, m), 7.15 (1H, m), 6.85 (1H, t, J = 7Hz), 4.15 (2H, s). ESI-TOF HRMS m/e 343.1647 ($C_{21}H_{18}N_4O$ + H^+ requires 343.1559).
15. **1a** λmax 330 nm (ε 5900 $M^{-1}cm^{-1}$), 229 (ε 28,900 $M^{-1}cm^{-1}$). At 254 nm, which is not a maximum, ε = 21,400 $M^{-1}cm^{-1}$. Other 2-aryl derivatives were found to have very similar λmax and εmax values. The yields and purities of cycloalkyl derivatives **2c** and **3e** were calculated from LC calibrations conducted using 2-cyclohexyl-3-benzylaminoimidazo[1,2-a]pyridine.[6] All products were analyzed by LC-MS recorded on a Micromass Platform LC in positive ion ESI mode. LC conditions: C-18 column, linear gradient from 90% A 10% B to 100% B over 10 min. where A was 5mM NH_4OAc in H_2O and B was 5mM NH_4OAc in MeCN. Selected compounds were characterized by ^1H nmr high resolution ESI-TOF mass spectrometry for example: **1c** m/e 344.1530 ($C_{20}H_{17}N_5O$ + H^+ requires 344.1511); **3b** m/e 296.1496 ($C_{16}H_{17}N_5O$ + H^+ requires 296.1511).
16. 3-Carboxybenzaldehyde (0.29 g, 1.9 mmol) in DMF was activated by treatment with HATU (0.72g, 1.9 mmol) and DIEA (0.66ml, 3.8 mmol) and coupled to Rink amide resin 1.26g (loading 0.56 mmol/g). Reaction was complete within 30 min. An aliquot of resin was cleaved using TFA/CH_2Cl_2 (1:1) to give 3-carboxamidobenzaldehyde in quantitative yield by comparison of LC peak area with that of a standard. The resin-bound aldehyde (200mg, 0.1 mmol) in MeOH-CH_2Cl_2 (1:3) was treated with 2-aminopyridine (0.68 mmol) and scandium triflate (0.05 eq). After 1h benzylisonitrile (82 mg, 0.7 mmol) was added and the suspension shaken for 48 h at ambient temperature. The resin was washed with CH_2Cl_2, MeOH and CH_2Cl_2 and product was cleaved using two treatments with TFA/CH_2Cl_2 (1:1). The product was shown by LC-MS to be identical to **1a** prepared by the solution phase method.
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20. Prepared from 3,4-dimethoxyphenethylamine by formylation (ethylformate) then dehydration by reaction with phosgene and triethylamine followed by chromatography on basic alumina.