COMMUNICATION

ChemComm www.rsc.org/chemcomm

Traceless Fischer indole synthesis on the solid phase†

Claudia Rosenbaum,[a] Catherine Katzka,[a] Andreas Marzinzik[b] and Herbert Waldmann*[a]

[a] *Max-Planck-Institut für Molekulare Physiologie, Abteilung Chemische Biologie, Otto-Hahn-Str. 11, 44227 Dortmund, Germany and Universität Dortmund, Fachbereich 3, Organische Chemie, 44227 Dortmund, Germany. E-mail: herbert.waldmann@mpi-dortmund.mpg.de; Fax: +49/231/133-2499; Tel: +49/231/133-2400*

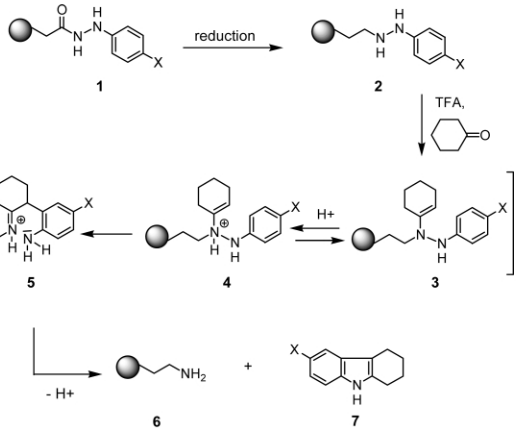
[b] *Novartis Pharma AG, CCU/CT Combinatorial Chemistry, WSJ-507.509, 4002 Basel, Switzerland. E-mail: andreas.marzinzik@pharma.novartis.com; Fax: +41 61 324 6589; Tel: +41 61 324 6891*

Received (in Cambridge, UK) 15th May 2003, Accepted 17th June 2003
First published as an Advance Article on the web 1st July 2003

The Fischer indole synthesis using polymer-bound hydrazines is employed as the key step for the development of a traceless indole synthesis on a solid support.

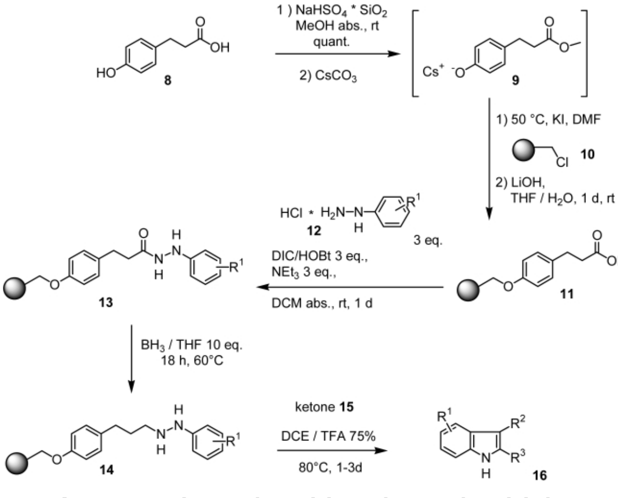
The combinatorial synthesis of small-molecule collections on polymeric supports is a powerful method for the discovery and development of new molecules with a predetermined profile of properties, in particular for subsequent application in chemical biology investigations and pharmaceutical research. Vital to success in this area is the development of synthetic methods that make the desired compounds available in an efficient and reliable manner. In this respect, methods which allow the detachment of the synthesized compounds from the resin without leaving behind traces of the solid-phase synthesis are of particular interest. They avoid the functional groups required for resin attachment remaining in the target molecules which may have an undesired effect on their biological activity. In addition, synthesis sequences are of particular interest where the desired products are formed and simultaneously released into solution in the last step of the synthesis, *i.e.* in the sense of a safety catch mechanism. Such a strategy ensures that only the desired compounds are released, unwanted side products not fulfilling the demand for safety catch release remain bound to a solid support. Equally if not more vital to success is the choice of the underlying molecular framework of the compound library. The hit rates in biological assays and the quality of the compounds are expected to be particularly high if the compound class in question can be regarded as biologically pre-validated,[1] in particular if they incorporate a so-called priviledged structure, *i.e.* a structure that mediates binding to multiple proteins.[2] In this regard, indoles represent one of the most important structural classes. A plethora of indole-based biologically active natural products and indole-derived drugs span an enormous range of biological activity.[3] Consequently, the combinatorial synthesis of indole libraries has received intense attention.[3–6]

We now report on the development of a traceless[5] solid phase indole synthesis employing the Fischer indole synthesis[6] as the key step. In planning the synthesis we envisioned generating hydrazines **2** on a solid support and treating them with appropriate ketones under typical conditions of the Fischer indole synthesis (Scheme 1). In the ensuing process an enamine **3** would be formed which upon protonation and [3,3]-sigmatropic rearrangement would give rise to an iminium intermediate **5**. Intramolecular attack of the formed aniline nitrogen would lead to traceless release of indole derivatives **7** from the polymeric carrier **6**. It was planned to generate the immobilized hydrazines **2** from polymer-bound hydrazides **1** by reduction of the hydrazide carbonyl group. Appropriately substituted hydrazides **1** are compatible with a variety of organic-chemical transformations like Pd(0)-catalyzed sp²–sp²-coupling processes, Grignard reactions and Wittig olefinations.[7] Surely they open up the opportunity to establish highly diverse compound libraries. The plan for the synthesis was executed as shown in Scheme 2.



Scheme 1 Plan for the development and proposed mechanism of the traceless Fischer indole synthesis on a solid support.

Initially *p*-hydroxyphenylpropionic acid **8** was converted into the methyl ester which was deprotonated to give phenolate **9**.[8] Nucleophilic attack on Merrifield resin **10** (resin loading 1.1 mmol g^{-1}) in the sense of a Williamson ether synthesis and saponification of the methyl ester yielded polymer-bound carboxylic acid **11** (resin loading 0.78 mmol g^{-1}, determined by coupling with H-lysine(Fmoc)-OH and UV-spectrometric quantification of the Fmoc group attached to the resin). This polymer–linker conjugate was then converted into substituted immobilized hydrazide **13** employing diisopropylcarbodiimide (DIC) and *N*-hydroxybenzotriazole (HOBt) as condensing reagents. Reduction of hydrazide **13** to hydrazine **14** was best accomplished by treatment with 10 equiv. of the BH_3·THF complex at 60 °C overnight. Formation of the hydrazines was



Scheme 2 Traceless Fischer indole synthesis in the solid phase.

---

† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b305497g/

DOI: 10.1039/b305497g

ascertained by means of high resolution magic angle spinning (MAS) NMR-spectroscopic investigation[9] of resin **14** (R^1 = Br). An HMQC experiment allowed for unambiguous establishment of a C/H correlation characteristic for a polymer-bound hydrazine (Fig. 1). Alternative reduction to an immobilized hydrazone which might react with a ketone in the presence of traces of water to a new hydrazone released into solution before undergoing a subsequent Fischer rearrangement (Scheme 3) was not detected.

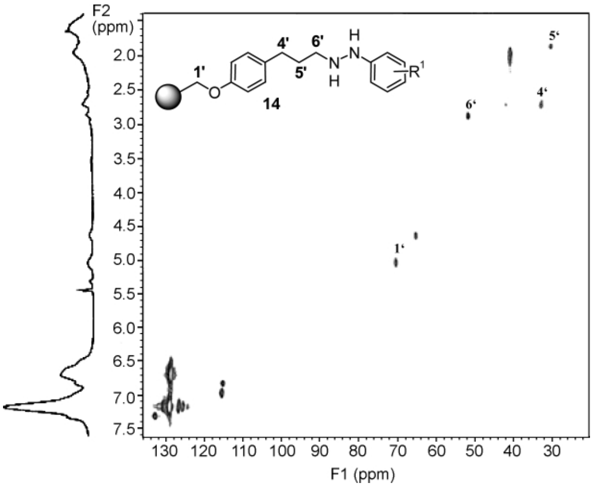
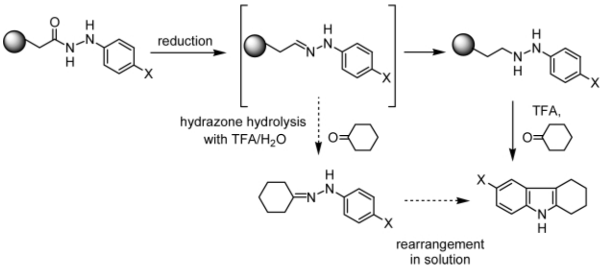


Fig. 1 HMQC-NMR spectrum of the polymer-bound hydrazine **14**.



Scheme 3 Possible pathways for formation and traceless release of the indoles.

Polymer-bound hydrazines **14** were suspended in a mixture of dichloroethane/trifluoroacetic acid (1 : 3), and after addition of a ketone **15** the mixture was shaken at 80 °C for 1–3 days (Scheme 2). The building blocks employed in the traceless indole synthesis are shown in Fig. 2, *i.e.* differently substituted hydrazines and ketones were chosen.

Notably, in both cases functional groups are present which allow for further structural modification of the obtained indoles, *i.e.* an aromatic bromide or keto groups. The results of the synthesis are shown in Fig. 3. In total eleven compounds were synthesized enabling use of all building blocks chosen. The overall yield from attachment of the hydrazine on a solid support to release of the desired indole into solution vary from 6 to 41% after chromatographic separation.

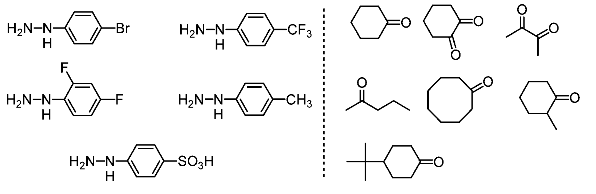


Fig. 2 Building blocks employed in the solid phase synthesis.

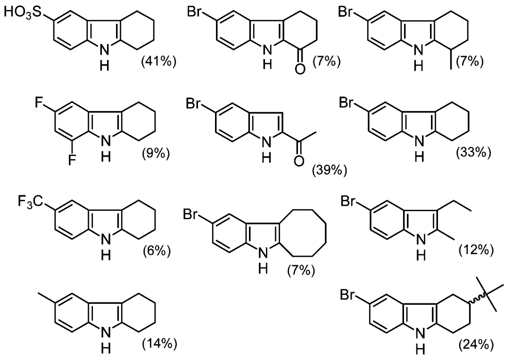


Fig. 3 Results of the traceless Fischer indole synthesis.

Immediately after the traceless synthesis, the indole derivatives are isolated in approx. 80% purity. After chromatographic separation they were obtained with a purity of 99%. The results show that the solid phase sequence tolerates several different functional groups and that it delivers the desired products in a very straightforward and practical manner. Mono- and disubstituted aryl hydrazines as well as mono- and di-keto compounds were successfully used.

In conclusion we have developed a traceless indole synthesis on a solid support. It employs the Fischer indole rearrangement as a key step, is operationally very practical, tolerant to a variety of functional groups in both types of building blocks and makes the desired compounds available in preparatively useful overall yields and with high purity.

This research was supported by the Max Planck Gesellschaft and the Fonds der Chemischen Industrie. C. R. is grateful to the Landesgraduiertenstiftung Baden-Württemberg for financial support.

Notes and references

1 R. Breinbauer, I. R. Vetter and H. Waldmann, *Angew. Chem.*, 2002, **114**, 3002–3015 (*Angew. Chem., Int. Ed.*, 2002, **41**, 2878–2890).

2 B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235–2246.

3 For reviews on the indole ring as a priviledged structure and combinatorial synthesis of indole-based compound libraries see: (*a*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930; (*b*) S. Bräse, C. Gil and K. Knepper, *Bioorg. Med. Chem.*, 2002, **10**, 2415–2437.

4 S.-H. Lee, B. Clapham, G. Koch, J. Zimmermann and K. D. Janda, *J. Comb. Chem.*, 2003, **5**, 188–196. This paper contains a compilation of various indole syntheses on the solid phase.

5 For a traceless indole synthesis on a solid support see: K. C. Nicolau, A. J. Roecker, R. Hughes, R. van Summeren, J. A. Pfefferkorn and N. Winssinger, *Bioorg. Med. Chem.*, 2003, **11**, 465–476.

6 For non-traceless Fischer indole syntheses on a solid support see: (*a*) S. M. Hutchins and K. T. Chapman, *Tetrahedron Lett.*, 1996, **37**, 4869–4872; (*b*) L. Yang, *Tetrahedron Lett.*, 2000, **41**, 6981–6984; (*c*) L. C. Cooper, G. G. Chicchi, K. Dinnell, J. M. Elliott, G. J. Hollingworth, M. M. Kurtz, K. L. Locker, D. Morrison, D. E. Shaw, K.-L. Tsao, A. P. Watt, A. R. Williams and C. J. Swain, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1233–1236; (*d*) J. Tois, R. Franzèn, O. Aitio, K. Huikko and J. Taskinen, *Tetrahedron Lett.*, 2000, **41**, 2443–2446.

7 (*a*) F. Stieber, U. Grether and H. Waldmann, *Angew. Chem.*, 1999, **111**, 1142–1145 (*Angew. Chem., Int. Ed.*, 1999, **38**, 1073–1077); (*b*) F. Stieber, U. Grether and H. Waldmann, *Chem. Eur. J.*, 2003, **9**, in press; (*c*) F. Stieber, R. Mazitschek, N. Soric, A. Giannis and H. Waldmann, *Chem. Eur. J.*, 2003, **9**, in press.

8 B. Das, B. Venkataiah and P. Madhusudhan, *Synlett*, 2000, 59–60.

9 MAS-NMR measurements: Varian Mercury 400, gHX Nano Probe Probehead, 400 MHz, spin rate of 2.5 kHz.