ORGANIC LETTERS

2003
Vol. 5, No. 16
2919−2922

Microwave-Assisted Solid-Phase Organic Synthesis (MASPOS) as a Key Step for an Indole Library Construction†

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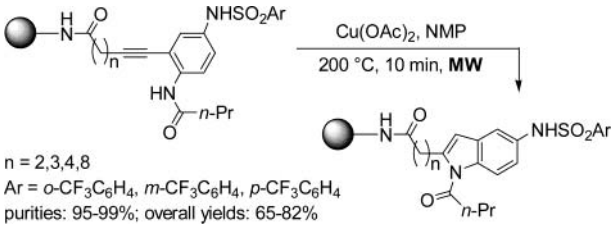
Received June 11, 2003

ABSTRACT



Microwave-assisted solid-phase organic synthesis (MASPOS) has been demonstrated to significantly facilitate the Cu(II)- or Pd(II)-mediated ring closure of the resin-bound 2-alkynylanilides. Under microwave irradiation at 200 °C [for $Cu(OAc)_2$, NMP] or 160 °C [for $Pd(MeCN)_2Cl_2$, THF] for 10 min, 1-acyl-2-alkyl-5-arenesulfamoylindoles were obtained, after cleavage from the resin, in 95–99% purities and in 65–82% overall yields via a 5-step synthetic sequence.

Microwave-assisted organic synthesis[1] has gained increasing popularity in recent years due to advancement in instrumentation. Organic reactions can now be performed in closed vessels in a temperature and pressure controlled manner, providing reproducible results. The short reaction time normally attained at high temperature under microwave superheating is ideally suited for combinatorial chemistry in drug discovery.[2] In the solid-phase combinatorial synthesis,[3] polymeric resins are used to facilitate separation of products. However, because of the heterogeneous nature of organic reactions occurring at the interface of polymeric support and solution, it often requires a long reaction time or results in incomplete conversion of starting materials. The latter accumulates impurities on resins and diminishes the quality of compound libraries. It has been demonstrated that microwave dielectric heating can be used to speed up organic

† Dedicate to Prof. Xian Huang of the Department of Chemistry, Zhejiang University, China, on the occasion of his 70th birthday.

(1) For recent monographies and reviews, see: (a) Hayes, B. L. *Microwave Synthesis: Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002. (b) *Microwaves in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH: New York, 2002. (c) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199−9223. (d) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283.

(2) For recent reviews on microwave-assisted combinatorial chemistry, see: (a) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95−105. (b) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314−320. (c) Wilson, N. S.; Roth, G. P. *Curr. Opin. Drug Discov. Dev.* **2002**, *5*, 620−629. (d) Wathey, B.; Tiemey, J.; Lidström, P.; Westman, J. *Drug Discov. Today* **2002**, *7*, 373−380. (e) Lidstrom, P.; Westman, J.; Lewis, A. *Comb. Chem. High Throughput Screen.* **2002**, *5*, 441−458. (f) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251−1283. (g) Blackwell, H. E. *Org. Biomol. Chem.* **2003**, *1*, 1251−1255.

(3) (a) Obrecht, D.; Villalgordo, J. M. *Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries*; Pergamon: Oxford, UK, 1998. (b) *Combinatorial Chemistry: Synthesis, Analysis, Screening*; Jung, G., Ed.; Wiley-VCH: Weiheim, Germany, 1999. (c) *Combinatorial Chemistry: A Practical Approach*; Bannwarth, W., Felder, E., Eds.; Wiley-VCH: Weiheim, Germany, 2000. (d) *Solid-Phase Organic Synthesis*; Burgess, K., Ed.; Wiley-Interscince: New York, 2000. (e) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; Wiley-Interscience: New York, 2000. (f) Dorwald, F. Z. *Organic Synthesis on Solid Phase: Supports, Linkers, Reactions*; Wiley-VCH: Weiheim, Germany, 2000. (g) *Combinatorial Library: Methods and Protocols*; Bellavance, L., Ed.; Humana Press: Totowa, NJ, 2002. (h) *Handbook of Combinatorial Chemistry*; Nicolaou, K. C., Hanko, R., Hartwig, W., Eds.; Wiley-VCH: Weiheim, Germany, 2002. (i) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091−2157. (j) Dolle, R. E. *J. Comb. Chem.* **2002**, *4*, 369−418 and cited previous articles in this series.

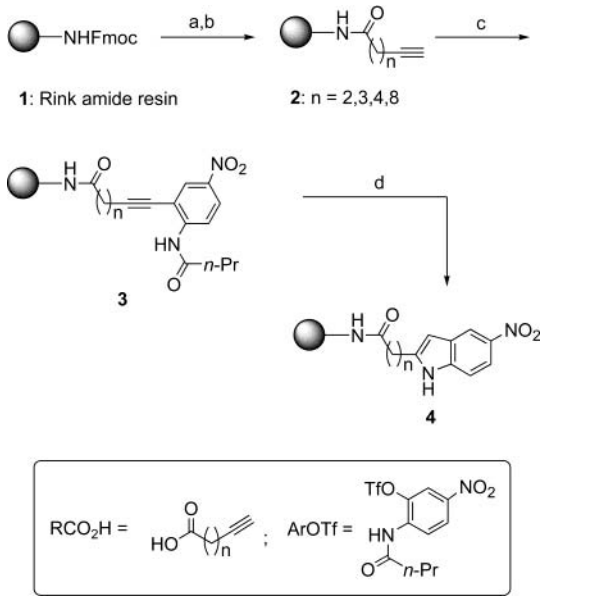
10.1021/ol0350543 CCC: $25.00
Published on Web 07/11/2003

reactions carried out on soluble[4] and solid[5−7] polymeric supports. We report here on an indole library synthesis using microwave-assisted solid-phase organic synthesis (MASPOS)[8] as a solution for promoting a metal-catalyzed cyclization of the resin-bound 2-alkynylanilides, which fails under thermal heating conditions.

The indole ring system is an attractive scaffold for combinatorial synthesis.[9] It increases structural diversity via ring substitution and diverse biological activities are associated with indole-derived drug-like molecules. A survey of the literature revealed that solid-phase synthesis of the indole library possessing an arenesulfamoyl group on the ring skeleton has not been reported.[10] We envisaged a solid-phase split-and-pool approach using the directed sorting method to construct a library of sulfonamides[11] engineered on the indole scaffold.[12] Scheme 1 illustrates the synthesis of the resin-bound 5-nitroindoles **4**, using the IRORI radio frequency (R_f)-encoded MicroKan reactors. The 2-alkynylanilides **3** were prepared via the Pd(0)−Cu(I)-catalyzed cross-coupling reaction of the resin-bound alkynes **2** with an aryl triflate prepared from 2-amino-5-nitrophenol.[12] *n*-Bu_4NI was used as an additive to facilitate the cross-coupling.[13] The structures of **3** were confirmed, after cleavage from the resin, by ^1H NMR to be of high purity and high yield. Treatment of **3** with *t*-BuOK in NMP[14] at room temperature afforded 5-nitroindoles **4** in ca. 80% yields estimated according to the initial loading of resin **1**. Unfortunately, reduction of the nitro group in **4** with $SnCl_2{\cdot}2H_2O$ could not completely form the desired amines, giving a mixture contaminated with the hydroxyamine intermediates.[15]

Alternatively, reduction of nitrobenzamides **3** was successfully achieved with a 1 M solution of $SnCl_2{\cdot}2H_2O$ to furnish amines **5** in excellent yields and purities (Scheme 2). Treatment of **5** with excess $ArSO_2Cl$ in pyridine−CH_2Cl_2 mixed solvent gave the resin-bound sulfonamides **6**. However, difficulty was encountered again in the cyclization of **6** under a variety of conditions used for solution reactions. These include the following: (a) *t*-BuOK (5−10 equiv) in DMF at 80 °C for 24 h;[14] (b) *n*-Bu_4NF (10 equiv) in THF, 80 °C for 24 h;[16] and (c) $Cu(OAc)_2$ (1 equiv) in DCE at 85 °C for 24 h (entry 5, Table 1).[17] The materials recovered

Scheme 1. Synthesis of 5-Nitroindoles **4** via Base-Catalyzed Cyclization[a]



[a] Reagents and conditions: (a) 20% piperidine, DMF, rt, 1 h; (b) RCO_2H (5.0 equiv), DIC (5.0 equiv), HOBt (5.0 equiv), DMF−DCM (1:1), rt, 1 h; (c) ArOTf (5.0 equiv), $Pd(PPh_3)_4$ (10 mol %), CuI (20 mol %), *n*-Bu_4NI (1.5 equiv), DMF−Et_3N (5:1), rt, 24 h; (d) *t*-BuOK (5.0 equiv), NMP, rt, 10 h (∼80% from **1**).

(4) (a) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885−3890. (b) Jacques, J.; Eynde, V.; Rutot, D. *Tetrahedron* **1999**, *55*, 2687−2694. (c) Porcheddu, A.; Ruda, G. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2003**, 907−912.

(5) For peptide synthesis and cleavage, see: (a) Yu, H.-M.; Chen, S.-T.; Chiou, S.-H.; Wang, K.-T. *J. Chromatogr.* **1988**, *456*, 357−362. (b) Yu, H.-M.; Chen, S.-T.; Wang, K.-T. *J. Org. Chem.* **1992**, *57*, 4781−4784. (c) Erdelyi, M.; Gogoll, A. *Synthesis* **2002**, 1592−1596.

(6) (a) Gong, Y.-D.; Sohn, H.-Y.; Kurth, M. J. *J. Org. Chem.* **1998**, *63*, 4854−4856. (b) Chandrasekhar, S.; Padmaja, M. B.; Raza, A. *Synlett* **1999**, 1597−1599. (c) Hoel, A. M. L.; Nielsen, J. *Tetrahedron Lett.* **1999**, *40*, 3941−3944. (d) Yu, A.-M.; Zhang, Z.-P.; Yang, H.-Z.; Zhang, C.-X.; Liu, Z. *Synth. Commun.* **1999**, *29*, 1595−1599. (e) Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 515−519. (f) Kumar, H. M. S.; Anjaneyulu, S.; Reddy, B. V. S.; Yadav, J. S. *Synlett* **2000**, 1129−1130. (g) Stadler, A.; Kappe, C. O. *Eur. J. Org. Chem.* **2001**, 919−925. (h) Stadler, A.; Kappe, C. O. *Tetrahedron* **2001**, *57*, 3915−3920. (i) Yang, H.; Peng, Y.; Song, G.; Qian, X. *Tetrahedron Lett.* **2001**, *42*, 9043−9046. (j) Deng, Y.; Hlasta, D. J. *Org. Lett.* **2002**, *4*, 4017−4020. (k) Olivos, H. J.; Alluri, P. G.; Reddy, M. M.; Salony, D.; Kodadek, T. *Org. Lett.* **2002**, *4*, 4057−4059. (l) Strohmeier, G. A.; Kappe, C. O. *J. Comb. Chem.* **2002**, *4*, 154−161. (m) Petricci, E.; Botta, M.; Corelli, F.; Mugnaini, C. *Tetrahedron Lett.* **2002**, *43*, 6507−6509. (n) Austin, R. E.; Okanya, J. F.; Bond, D. R. S.; Al-Obeidi, F. *Tetrahedron Lett.* **2002**, *43*, 6169−6171. (o) Yaylayan, V. A.; Siu, M.; Bélanger, J. M. R.; Paré, J. R. J. *Tetrahedron Lett.* **2002**, *43*, 9023−9025. (p) Hoener, A. P. F.; Henkel, B.; Gauvin, J.-C. *Synlett* **2003**, 63−66. For a SPOT-synthesis, see: (q) Scharn, D.; Wenschuh, H.; Reineke, U.; Schneider-Mergener, J.; Germeroth, L. J. *Comb. Chem.* **2000**, *2*, 361−369.

(7) For metal-catalyzed reactions, see: (a) Larhed, M.; Lindeberg, G.; Hallberg, A. *Tetrahedron Lett.* **1996**, *37*, 8219−8222. (b) Combs, A. P.; Saubern, S.; Rafalski, M.; Lam, P. Y. S. *Tetrahedron Lett.* **1999**, *40*, 1623−1626. (c) Kaiser, N.-F. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3595−3598. (d) Alterman, M.; Hallberg, A. J. *Org. Chem.* **2000**, *65*, 7984−7989. (e) Fînaru, A.; Berthault, A.; Besson, T.; Guillaumet, G.; Berteina-Raboin, S. *Org. Lett.* **2002**, *4*, 2613−2615.

(8) Microwave-assisted solid-phase organic synthesis (MASPOS) is used here for the organic reactions of resin-bound substrates performed in solvent at defined temperature under microwave irradiation. Microwave-assisted organic synthesis with inorganic supports, dry media, or under solventless conditions falls into a different category.

(9) For reviews, see: (a) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472. (b) Franzén, R. G. *J. Comb. Chem.* **2000**, *2*, 195−214. (c) Krchňák, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61−91. (d) Brase, S.; Gil, C.; Knepper, K. *Biorg. Med. Chem.* **2002**, *10*, 2415−2437.

(10) For solution synthesis, see: (a) Owa, T.; Yoshino, H.; Okauchi, T.; Yoshimatsu, K.; Ozawa, Y.; Sugi, N. H.; Nagasu, T.; Koyanagi, N.; Kitoh, K. *J. Med. Chem.* **1999**, *42*, 3789−3799. (b) Owa, T.; Okauchi, T.; Yoshimatsu, K.; Sugi, N. H.; Ozawa, Y.; Nagasu, T.; Koyanagi, N.; Okabe, T.; Kitoh, K.; Yoshino, H. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1223−1226.

(11) For a review on anticancer and antiviral sulfonamides, see: Scozzafava, A.; Owa, T.; Mastrolorenzo, A.; Supuran, C. T. *Curr. Med. Chem.* **2003**, *10*, 925−953.

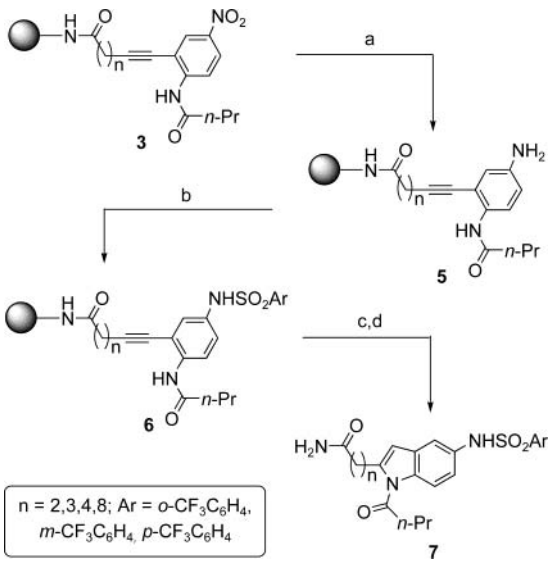
(12) For solution synthesis, see: Dai, W.-M.; Sun, L.-P.; Guo, D.-S. *Tetrahedron Lett.* **2002**, *43*, 7699−7702.

(13) Dai, W.-M.; Guo, D.-S.; Sun, L.-P. *Tetrahedron Lett.* **2001**, *42*, 5275.

(14) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488−2490.

(15) For reduction of 5-nitroindole on Wang resin, see: Tois, J.; Franzén, R.; Aitio, O.; Huikko, K.; Taskinen, J. *Tetrahedron Lett.* **2000**, *41*, 2443−2446. Purification of the end product was carried out.

Scheme 2. Synthesis of Indoles via Cu(II)- or Pd(II)-Mediated Cyclization[a]

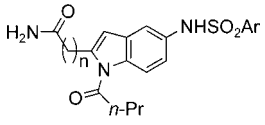


[a] Reagents and conditions: (a) $SnCl_2 \cdot 2H_2O$ (50.0 equiv, 1.0 M), NMP, rt, 24 h; (b) $ArSO_2Cl$ (5.0 equiv), pyridine−DCM (1:5), rt, 20 h; (c) $Cu(OAc)_2$ (1.0 equiv), NMP, 200 °C, 10 min, MW or $Pd(MeCN)_2Cl_2$ (0.2 equiv), THF, 160 °C, 10 min, MW; (d) 20% TFA in DCM, rt, 1 h (see Tables 1 and 2).

from the above reactions, after treatment with 20% TFA in DCM, are mainly the uncyclized 2-alkynylanilides. Because the MicroKan reactors are not suited for temperatures higher than 85 °C, the resin-bound **5** in each reactor was then transferred to a 5-mL Emrys process vial together with the R_f tag for preserving the structural information of the individual library member.[18] MASPOS was then performed on an Emrys creator from Personal Chemistry AB. Table 1 summarizes the results of the Cu(II)- and Pd(II)-mediated cyclization of **6**. Under thermal heating below 80 °C for 240−300 min, partial cyclization took place with catalytic $Pd(MeCN)_2Cl_2$ [19] to give indole **7** in <80% purities (entries 1−2, Table 1). In contrast, under microwave dielectric heating,[20] **6** cyclized at 160 °C (THF, 10 min) in the presence of 0.2 equiv of $Pd(MeCN)_2Cl_2$ to afford **7** in 75% overall yield from **1** and in 94% purity. However, replacement of THF with NMP (180 °C, 10 min) decreased both the yield (61%) and purity (85%) of **7**, presumably due to cleavage of the product from the resin (entry 3 vs entry 4). For the microwave-assisted $Cu(OAc)_2$-promoted cyclization, the best results (82% yield and 98% purity) were obtained in NMP at 200 °C for 10 min. Lower reaction temperature (entries 6 and 7 vs entry 8) or less catalyst loading (entry 9 vs entry 8) diminished the yield and purity.

After optimization of the cyclization conditions under microwave irradiation, a small library of 12 indoles **7** was synthesized with MASPOS as the key step via the 5-step synthetic sequence (**1** → **2** → **3** → **5** → **6** → **7**).[21] Table 2 shows two sets of results with Pd(II) and Cu(II) as the catalyst, respectively. In all cases, purities of >95% for the crude products **7** were obtained with estimated overall yields

Table 1. Cyclization Results of Resin-Bound 2-Alkynylanilides **6** with or without Microwave Irradiation

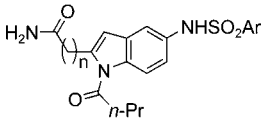


7

entry	Ar/*n*	cat.;[a] *T* (°C)/*t* (min)	yield/purity (%)[b]
1	*p*-$CF_3C_6H_4$/2	Pd(II)(0.1); 75/300[c]	65/75
2	*p*-$CF_3C_6H_4$/8	Pd(II)(0.5); 80/240[d]	70/80
3	*p*-$CF_3C_6H_4$/8	Pd(II)(0.2); 160/10[e,g]	75/94
4	*m*-$CF_3C_6H_4$/4	Pd(II)(0.2); 180/10[c,g]	61/85[h]
5	*p*-$CF_3C_6H_4$/3	Cu(II)(1.0); 85/1440[f]	*i*
6	*o*-$CF_3C_6H_4$/2	Cu(II)(1.0); 160/15[e,g]	56/70
7	*m*-$CF_3C_6H_4$/3	Cu(II)(1.0); 180/10[f,g]	68/70
8	*m*-$CF_3C_6H_4$/2	Cu(II)(1.0); 200/10[c,g]	82/98
9	*o*-$CF_3C_6H_4$/3	Cu(II)(0.2); 200/15[c,g]	70/80

[a] Pd(II) = $Pd(MeCN)_2Cl_2$; Cu(II) = $Cu(OAc)_2$. [b] Yield was calculated based on loading of the commercial resin **1**. Purity was estimated by ^1H NMR of the crude product mixture. The major impurity is the unreacted substrate. [c] In NMP. [d] In DMF. [e] In THF. [f] In DCE. [g] With microwave irradiation. [h] Unidentified impurity was detected. [i] The substrate was recovered.

Table 2. Synthesis of Indoles **7** via Microwave-Assisted Cyclization of Resin-Bound 2-Alkynylanilides **6**



7

entry	*n*	Ar	yield (%)[a]	purity (%)[b]
20 mol % $Pd(MeCN)_2Cl_2$, THF, 160 °C, 10 min, MW				
1	2	*o*-$CF_3C_6H_4$	70	99
2	4	*o*-$CF_3C_6H_4$	71	99
3	8	*o*-$CF_3C_6H_4$	65	99
4	4	*m*-$CF_3C_6H_4$	71	99
5	8	*m*-$CF_3C_6H_4$	68	99
100 mol % $Cu(OAc)_2$, NMP, 200 °C, 10 min, MW				
6	3	*o*-$CF_3C_6H_4$	72	95
7	2	*m*-$CF_3C_6H_4$	82	98
8	3	*m*-$CF_3C_6H_4$	75	96
9	2	*p*-$CF_3C_6H_4$	74	95
10	3	*p*-$CF_3C_6H_4$	71	96
11	4	*p*-$CF_3C_6H_4$	70	97
12	8	*p*-$CF_3C_6H_4$	72	95

[a] Calculated based on loading of the commercial resin **1**. [b] Determined by HPLC. The structure was confirmed by ^1H NMR and MS.

(16) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529−534.

(17) (a) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. *Tetrahedron Lett.* **1995**, *36*, 7841−7844. (b) Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* **2002**, *43*, 1277−1280.

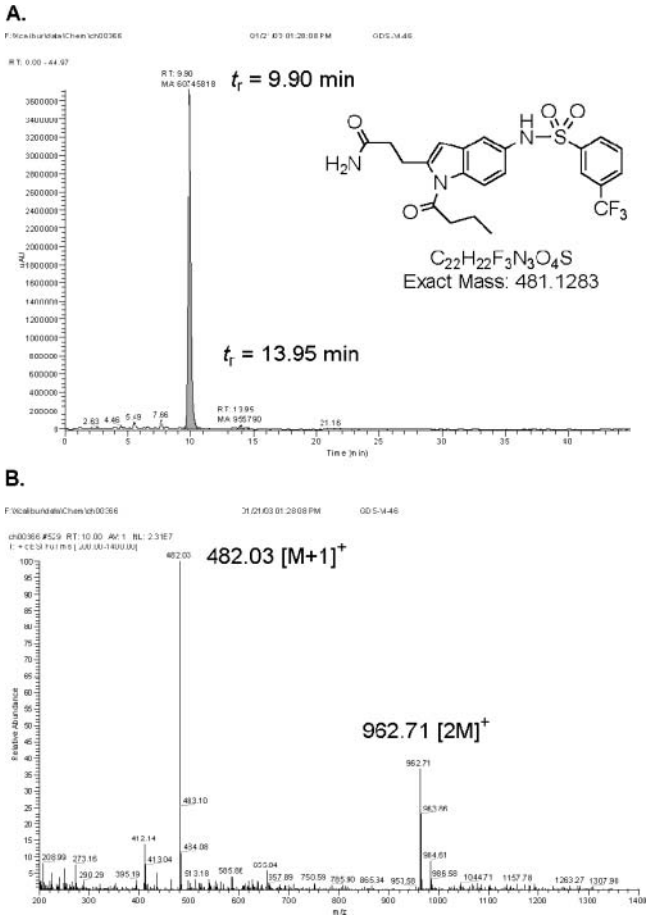


Figure 1. LC-MS data for indole **7** (n = 2, Ar = m-$CF_3C_6H_4$). (A) HPLC chromatogram showing a major peak at t_r = 9.90 min (98% purity). (B) Mass spectrum of the major peak in panel A, showing a base peak at m/z 482 $[M + 1]^+$ and a $[2M]^+$ peak corresponding to m/z 962. Also see Supporting Information for larger copies.

of 65−82% calculated from the commercial Rink amide resin **1**. All members of the library were characterized by LC-MS analysis and the molecular structures of **7** were confirmed by ^{1}H NMR. Figure 1 illustrates the typical HPLC chart of an unpurified indole **7** and the MS spectrum of the major elute. LC-MS data of other indoles **7** are found in the Supporting Information.

In summary, we have described above a new example of MASPOS applied to the first solid-phase synthesis of a C5 arenesulfamoyl-substituted indole compound library. It features a combination of microwave-assisted fast organic reaction with solid-phase combinatorial chemistry technology for production of high-quality single-molecule libraries. We are currently expanding the size of the indole library by using various $ArSO_2Cl$ for the formation of sulfonamides **6**. Our preliminary results indicated that the microwave-assisted Cu(II)-mediated ring closure of **6** tolerates a variety of functional groups in the sulfonamide subunit, including the F-, Cl-, MeO-, CF_3O-, and alkyl-substituted phenyl, naphthyl, and thiophenyl groups. The details will be disclosed in due course.

Acknowledgment. The work was financially supported in part by the Innovation and Technology Fund (ITS/119/00) from the Innovation and Technology Commission of the Hong Kong Special Administrative Region, China. We also thank HKUST for providing a Postdoctoral Fellowship Matching Fund to D.-S. Guo, and the Department of Chemistry, HKUST, for purchasing the Emrys creator and for providing a Visiting Scholarship to X.-H. Huang.

Supporting Information Available: Experimental procedures and LC-MS analysis and ^{1}H NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0350543

(18) Caution: The encoded R_f tag cannot be archived after exposure to microwave if the tag vertically sits in a 2-mL process vial. The reason is not known. Photos of the reaction vials are found in the Supporting Information.

(19) van Esseveldt, B. C. J.; van Delft, F. L.; de Gelder, R.; Rutjes, F. P. J. T. *Org. Lett.* **2003**, *5*, 1717−1720 and references therein.

(20) Decomposition of the resin at the reaction temperatures as high as 200 °C was not observed. Also, see refs 6g,n and 7c,d.

(21) For a recent solid-phase indole synthesis with microwave irradiation, see ref 7e.