Available online at www.sciencedirect.com

ScienceDirect

Tetrahedron Letters 48 (2007) 9144–9147

Tetrahedron Letters

Synthesis and characterization of aryl thioacetyl styrene monomers: towards a new generation of SERS-active polymers

Baker Jawabrah Al-Hourani, Juan P. Bravo-Vasquez, L. R. Hermann High and Hicham Fenniri*

National Institute for Nanotechnology and Department of Chemistry, University of Alberta 11421 Saskatchewan Drive, Edmonton, Alberta, Canada T6G 2M9

Received 10 October 2007; revised 21 October 2007; accepted 23 October 2007
Available online 26 October 2007

Abstract—A new family of thioacetyl styrene derivatives was synthesized in good isolated yields for the preparation of spectroscopically-encoded SERS-active polymers.

The barcoded resins (BCRs) are spectroscopically encoded polymers with unique Raman and infrared vibrational spectra.[1] Each BCR may be used as a carrier for a small molecule or a receptor and used in encoded combinatorial screening or as a high-throughput diagnostic tool, respectively. Because of their unique polymeric matrix composition, the BCRs may be simultaneously identified using hyperspectral[2] and/or time-of-flight secondary ion mass spectrometry[3] imaging/mapping. To expand the repertoire of BCRs, we have also shown that over 600 BCRs may be produced from a small set of unique styrene monomers.[4] While we are currently developing useful applications for this technology platform, we are also looking at our next challenges. In particular, we envision that the combination of Raman spectroscopy and flow cytometry[5] would not only allow us to implement directed sorting[6] strategies for library synthesis but would also dramatically expedite BCR identification, screening, and sorting. Although Raman spectroscopy is limited by its low signal to noise ratio, we have been able to record reliable spectra of the BCRs in 10 ms using state-of-the-art instrumentation,[2] which could translate to a screening speed of 10–100 beads/s under optimal conditions. To further push this limit and reduce the cost associated with the Raman detection set-up, we opted to design a new family of BCR–metal nanoparticle (BCR-NP) composites that can be detected with very high sensitivity using surface enhanced Raman scattering (SERS).[7] To take advantage of the SERS effect, the encoded polymer must be chemically or physically adsorbed on the surface of a SERS-active nanoparticle (silver or gold). To achieve this goal and impart high stability to the resulting BCR-NP composite we synthesized a new family of chemically stable mercapto-styrene co-monomers each with a unique vibrational signature (Chart 1). Because of their high affinity for metallic surfaces, we reasoned that the thiol groups would react with the nanoparticle surface to generate a self-assembled monolayer, which can then be copolymerized with a styrene monomer in a suspension polymerization set-up. In this Letter, we report the synthesis and characterization of a new family of thioacetyl-styrene monomers. We also discuss how their unique vibrational fingerprints could be modulated to generate a combinatorial library of SERS-active BCRs.

Flatt et al.[8] and de Boer et al.[9] have previously reported the synthesis of aryl thioacetyl derivatives by reacting aryl halides with 2 equiv the *n*-butyllithium (*n*-BuLi),

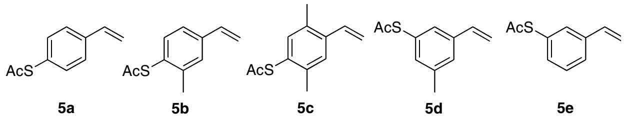
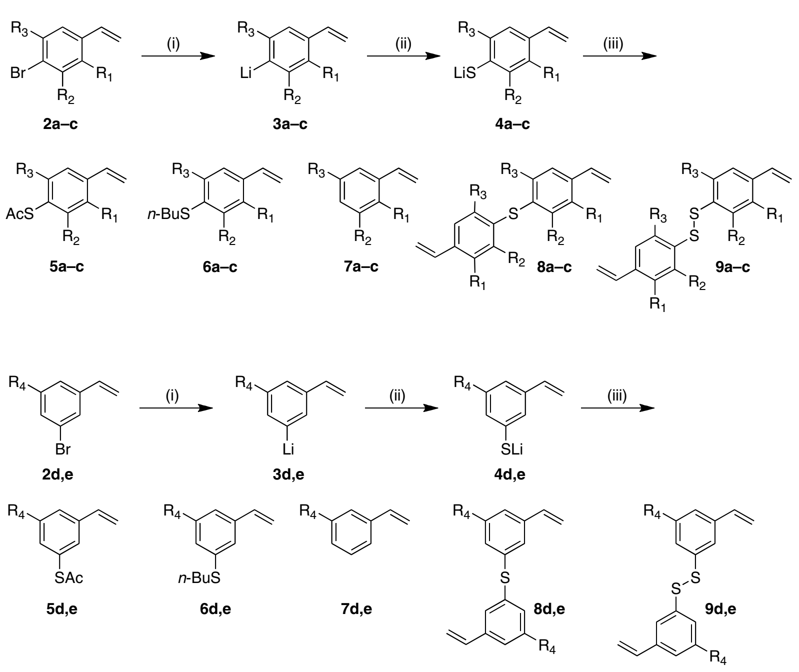


Chart 1. Target mercapto-styrene co-monomers.

Keywords: Styrene Monomers; Thioacetyls; Thiols; Sulfurs; Combinatorial chemistry; Barcoded polymers.

* Corresponding author. Tel.: +1 780 641 1750; fax: +1 780 641 1601; e-mail: Hicham.Fenniri@nrc-cnrc.gc.ca

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.118



Scheme 1. Reagents and conditions: Method 1: (i) *n*-BuLi (1.0 equiv), THF, −78 °C; (ii) S_8 (1 equiv), −78→20 °C; (iii) Ac_2O, −78 °C. Method 2: (i) *n*-BuLi (1.0 equiv), THF/petroleum ether (1:1), −78 °C; (ii) S_8 (1.0 equiv), −78 °C; (iii) Ac_2O (1.0 equiv), −78 °C, then H_2O/Et_2O. See Supplementary data for more detail.

followed by addition of sulfur (S_8), and trapping with acetyl chloride. de Boer et al. reported a yield of 33% whereas Flatt et al. stated that the synthesis proceeded in poor yield (7%). In our laboratories, reaction of bromostyrene **2a** with *n*-BuLi (1.0 equiv) at −78 °C followed by addition of S_8, warming up to 0 °C, then addition of acetyl chloride at −78 °C afforded the butylsulfide derivatives **6a** in 94% yield with no trace of the target thioacetyl **5a** (Scheme 1).[6] Compound **6a** is the product of S_N2 reaction between the lithium thiolate anion **3a** and by-product *n*-butylbromide. However, with 2 equiv of *n*-BuLi (to quench the *n*-butylbromide) thioacetyl **5a** did form but in poor yield (7%), in agreement with de Boer's report.[9] Jacob et al.[10] reported the synthesis of aryl thioacetyls from aryl iodide using *t*-butyllithium (*t*-BuLi), S_8, and acetyl chloride in 12–49% yields. Again, executing the reaction with *t*-BuLi, to avoid the reaction of thiolate anion **3a** with *n*-BuBr, gave neither compound **6a** nor the desired thioacetyl **5a**.

Here we developed a simple method to prepare *p*-mercaptostyrene derivatives **5a**–**e** (Chart 1) from aryl halides **2a**–**e** in very good yields (Chart 2). First, starting materials **2b**,[11–15] **2c**,[16,17] and **2d**[18,19] were synthesized in three steps each starting from aryl bromide derivatives **1b**–**d** (Chart 2) according to previously reported procedures in 78%, 71%, and 80% overall yields (three steps), respectively. All the reactions were monitored by GC–MS to determine the best reaction time and conditions. The synthetic strategy for the preparation of **5a**–**e** is shown in Scheme 1 and the results are summarized in Table 1. In fact the main difference with de Boer's reported strategy is that we have chosen a solvent system and optimized the reaction time to reduce by-product formation and enhance the yield of the target molecules.

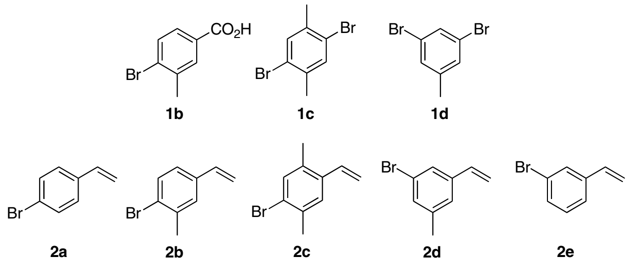


Chart 2.

Table 1. Yields of compounds **5**–**9** using Method 1 (Scheme 1)

	a	b	c	d	e
	$R_1 = H$ $R_2 = H$ $R_3 = H$	$R_1 = H$ $R_2 = CH_3$ $R_3 = H$	$R_1 = CH_3$ $R_2 = H$ $R_3 = CH_3$	$R_4 = CH_3$	$R_4 = H$
5	49 (74) 43^{a} $(70)^{a}$	30 (69) 23^{a} $(63)^{a}$	8 (74) 6^{a} $(69)^{a}$	37 (76) 32^{a} $(72)^{a}$	72 (74) 69^{a} $(72)^{a}$
6	1 (3)	0 (3)	3 (0)	2 (1)	0 (2)
7	0 (3)	7 (6)	1 (7)	3(2)	0 (5)
8	10 (11)	8 (12)	30 (16)	20 (15)	12 (14)
9	7 (2)	16 (4)	27 (0)	23 (0)	6 (0)

The numbers in bracket correspond to yields obtained using Method 2. All the yields are based on GC–MS data except for compounds **5a**–**d** for which the yield of isolated material is also given ([a]).

[a] Isolated yields.

Raman and SERS spectra were recorded on a Nicolet Almega system equipped with a CCD detector, an optical microscope, and a 780 nm excitation laser line. Spectra were collected in high-resolution mode in the

400–1900 cm^{-1} range with accumulation times ranging from 1 to 10 s. All measurements were made in backscattering geometry using a 10× microscope objective with a NA value of 0.90, providing scattering areas of 1 μm^2. Raman spectra of the monomers were directly recorded on the bulk material. Samples for SERS were prepared by casting 2 μL of an ethanolic solution of the monomer (10^{-4} M) on ~5 mm^2 area of a 9 nm mass thickness silver island film. The latter was prepared by physical vapor deposition on a glass substrate using a Kurt J. Lesker 4 pocket electron beam evaporation unit. During the film deposition the background pressure was 10^{-6} Torr, and the deposition rate (0.5 Å/s) was monitored using an XTC Inficon quartz crystal oscillator.[20] The Raman and SERS spectra were converted to a barcode by extracting the peak position for each particular monomer (Fig. 1).

Thioacetyl styrene monomers have the potential to facilitate the synthesis of functional copolymers, especially in applications in polymer-nanoparticle nanocomposites.[21] Surprisingly, no high yield synthesis of mercaptostyrene monomers has been reported. Our interest in developing a combinatorial family of copolymers drove us to optimize a high yielding strategy for their preparation. All the reactions were followed by GC–MS to determine the yield, product distribution, and optimal reaction time. Following Method 1,[9,10] the experiments were carried out under kinetically controlled conditions yielding thioacetyls **5b–d** in poor yields along with the formation of several by-products (**6–9**) (Table 1). However, the unsubstituted thioacetyls **5a**,**e** were obtained in 49% and 72% yields, respectively. Clearly, Method 1 was ineffective for the preparation of thioacetylated styrene monomers **5b–d** because the presence of the alkyl group on the benzene ring increases the reactivity of the intermediate thiolate anions in THF. To overcome this problem, the synthesis of thioacetyl styrene monomer **5b** was successfully achieved in a mixture of THF/petroleum ether (1:1) (Method 2) as a result of an improved solubility of sulfur and an enhanced stability[22] of the lithium intermediates **3** and **4**. As anticipated, the formation of the target compounds **5a–e**, was accomplished in good isolated yields of 70%, 63%, 69%, 72%, and 72%, respectively (Table 1). It is important to point out that the reaction scheme is also base-dependent. For instance, attempts at synthesizing the dialkylated thioacetyl **5c** monomer using *t*-BuLi instead of *n*-BuLi were unsuccessful, even at −50 °C. In contrast, *n*-BuLi led to the formation of lithium thiolate **4c** almost instantly at −75 °C following Method 1 and in ca. 3 min using Method 2.

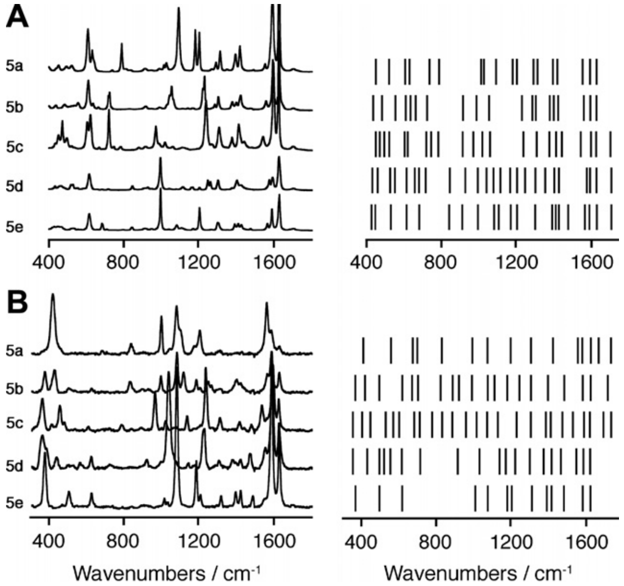


Figure 1. Raman (A) and SERS (B) spectra of compounds **5a–e** and their respective barcodes.

The defining characteristic of the BCRs is their preparation from spectroscopically active styrene monomers displaying unique IR and Raman vibrational fingerprints. The styrene monomers' substitution pattern is the source of spectral diversity of the resulting polymers. Compounds **5a–e** were selected on the basis of their (a) ability to form stable monolayers on metal nanoparticles (Ag, Au), (b) unique Raman and SERS spectral features, (c) relative chemical inertness, and (d) amenability to polymerization in a standard suspension polymerization reaction. Detailed analysis of the Raman and SERS spectra of each monomer resulted in a set of unique vibrations. These vibrations were converted into barcodes in which the position of each bar matches the peak wavenumber in the corresponding spectrum (Fig. 1).[1] The frequencies used to generate the barcodes are mainly due to aromatic ring skeletal bending and C–H stretching modes. We have previously established that the vibrational spectra (and barcodes) of the copolymers are, in all cases studied, a linear combination of the parent homopolymers' frequencies, in addition to new vibrations unique to the copolymers.[1] This result was critical in streamlining the choice of mercaptostyrene targets synthesized here and will be instrumental in the generation of a library of SERS-active BCRs from **5a–e**.[4]

In conclusion, we have developed an efficient strategy for the preparation of *p*-thioacetyl styrene derivatives in good yields with a reaction time of less than an hour. We have shown that this reaction sequence is particularly sensitive to temperature, solvent, and reaction time. In particular, stabilization of the aryl lithium intermediates was critical in improving the yield of the target compounds, and reducing by-product formation. We have also shown that the *p*-thioacetyl styrene derivatives have a significant SERS response when deposited on silver island films suggesting their possible application as spectroscopic tags, and more importantly for the generation of novel SERS-active polymers. This work is currently in progress and will be reported in due course.

Acknowledgments

We thank the National Research Council's Genomics and Health Initiative, the National Institute for Nanotechnology, the US National Institutes of Health (NIH EB03824), and the University of Alberta for supporting this program.

Supplementary data

Representative experimental procedures and spectroscopic data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.118.

References and notes

1. (a) Fenniri, H.; Ding, L.; Ribbe, A. E.; Zyrianov, Y. *J. Am. Chem. Soc.* **2001**, *123*, 8151–8152; (b) Fenniri, H.; Chun, S.; Ding, L.; Zyrianov, Y.; Hallenga, K. *J. Am. Chem. Soc.* **2003**, *125*, 10546–10560; (c) Raez, J.; Blais, D. R.; Zhang, Y.; Alvarez-Puebla, R. A.; Bravo-Vasquez, J. P.; Pezacki, J. P.; Fenniri, H. *Langmuir* **2007**, *23*, 6482–6485; (d) Bravo-Vasquez, J. P.; Alvarez-Puebla, R. A.; Fenniri, H. *Sens. Actuators, B* **2007**, *125*, 357–359.
2. (a) Fenniri, H.; Terreau, N.; Chun, S.; Oh, S. J.; Finney, W. F.; Morris, M. D. *J. Comb. Chem.* **2006**, *8*, 192–198; (b) Fenniri, H.; Hedderich, H. G.; Haber, K. S.; Achkar, J.; Taylor, B.; Ben-Amotz, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 4483–4485.
3. Chun, S.; Xu, J.; Cheng, J.; Ding, L.; Winograd, N.; Fenniri, H. *J. Comb. Chem.* **2006**, *8*, 18–25.
4. Fenniri, H.; Chun, S.; Terreau, O.; Bravo-Vasquez, J.-P. *J. Comb. Chem.* **2007**, *9*, in press, doi:10.1021/cc7001292.
5. (a) Gao, X.; Nie, S. *Anal. Chem.* **2004**, *76*, 2406–2410; (b) Drenski, M. F.; Mignard, E.; Alb, A. M.; Reed, W. F. *J. Comb. Chem.* **2004**, *6*, 710–716; (c) Trau, M.; Battersby, B. J. *Adv. Mater.* **2001**, *13*, 975–979; (d) *Flow Cytometry: A Practical Approach*; Ormerod, M. G., Ed.; Oxford University Press: New York, 2000; (e) *Flow Cytometry in Clinical Diagnosis*; Keren, D. F., McCoy, J. P., Jr., Carey, J. L., Eds.; ASCP Press: Chicago, 2001; (f) *Flow Cytometry and Cell Sorting*; Rudbruch, A., Ed.; Springer: New York, 2000.
6. (a) Nicolaou, K. C.; Xiao, X.-Y.; Parandoosh, Z.; Senyei, A.; Nova, M. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2289–2291; (b) Moran, E. J.; Sarshar, S.; Cargill, J. F.; Shahbaz, M. J. M.; Lio, A.; Mjalli, A. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1995**, *117*, 10787–10788; (c) Czarnik, T.; Nova, M. *Chem. Brit.* **1997**, *33*, 39–41.
7. (a) Aroca, R. F. *Surface Enhanced Vibrational Spectroscopy*; Wiley: New York, 2006; (b) Kneipp, K.; Kneipp, H.; Kneipp, J. *Acc. Chem. Res.* **2006**, *39*, 443–450.
8. Flatt, A. K.; Dirk, S. M.; Henderson, J. C.; Shen, D. E.; Su, J.; Reed, M. A.; Tour, J. M. *Tetrahedron* **2003**, *59*, 8555–8570.
9. De Boer, B.; Meng, H.; Perepichka, D. F.; Zheng, J.; Frank, M. M.; Chabal, Y. J.; Bao, Z. *Langmuir* **2003**, *19*, 4272–4284.
10. Ciszek, J. W.; Tour, J. M. *Tetrahedron Lett.* **2004**, *45*, 2801–2803.
11. Donya, A. P.; Pakter, M. K. *Ukrainskii Khimicheskii Zhurnal* (Russian edition) **1996**, *62*, 136–141.
12. Dawson, M. I.; Hobbs, P. D.; Derdzinski, K.; Chan, R. L.-S.; Gruber, J.; Chao, W.; Smith, S.; Thies, R. W.; Schif, L. J. *J. Med. Chem.* **1984**, *27*, 1516–1531.
13. (a) Combs, A. P.; Zhu, W.; Crawley, M. L.; Glass, B.; Polam, P.; Sparks, R. B.; Modi, D.; Takvorian, A.; McLaughlin, E.; Yue, E. W.; Wasserman, Z.; Bower, M.; Wei, M.; Rupar, M.; Ala, P. J.; Reid, B. M.; Ellis, D.; Gonneville, L.; Emm, T.; Taylor, N.; Yeleswaram, S.; Li, Y.; Wynn, R.; Burn, T. C.; Hollis, G.; Liu, P. C. C.; Metcalf, B. *J. Med. Chem.* **2006**, *49*, 3774–3789; (b) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Labaudiniere, R.; Airey, J. *J. Org. Chem.* **1999**, *64*, 1823–1830.
14. Jørgensen, M.; Krebs, F. C. *J. Org. Chem.* **2004**, *69*, 6688–6696.
15. (a) Quan, W.; Ma, J.; Peng, X.; Wu, T.; She, X.; Pan, X. *Tetrahedron: Asymmetry* **2005**, *16*, 2231–2234; (b) Vedejs, E.; Meier, G. P.; Snoble, K. A. J. *J. Am. Chem. Soc.* **1981**, *103*, 2823–2831.
16. (a) Donya, A. P.; Pakter, M. K. *Vysokomolekulyarnye Soedineniya, Seriya A i Seriya B* **1994**, *36*, 2068–2073; (b) Dokukina, A. F.; Koton, M. M.; Mineeva, O. K.; Paribok, V. A. *Zhurnal Obshchei Khimii* **1956**, *26*, 1849–1851; (c) Dokukina, A. F.; Koton, M. M.; Mineeva, O. K.; Paribok, V. A. *Zhurnal Obshchei Khimii* **1956**, *26*, 1651–1653.
17. (a) Brizius, G.; Pschirer, N. G.; Steffen, W.; Stitzer, K.; Loye, H.-C. Z.; Bunz, U. H. F. *J. Am. Chem. Soc.* **2000**, *122*, 12435–12440; (b) Yamamoto, K.; Ikeda, T.; Kitsuki, T.; Okamoto, Y.; Chikamatsu, H.; Nakazaki, M. *J. Chem. Soc., Perkin Trans. 1* **1990**, *2*, 271–276.
18. (a) Burke, E.A. *IEEE Trans. Nucl. Sci.* **1980**, *NS27*, 1760–1764; (b) Antuf'ev, V. V.; Dokukina, A. F.; Votinov, M. P.; Suntsov, E. V.; Boldyrev, A. G. *Vysokomolekulyarnye Soedineniya* **1965**, *7*, 380–384; (c) Nakazaki, M.; Yamamoto, K.; Ikeda, T.; Kitsuki, T.; Okamoto, Y. *J. Chem. Soc., Chem. Commun.* **1983**, *14*, 787–788.
19. (a) Hiroshi, U.; Takashi, S.; Kouichi, A.; Susumu, K.; Hisashi, S.; Takahisa, M.; Yasumasa, K.; Tomoko, O.; Yuki, S.; Iichiro, K. PCT Int. Appl. 2007 058 392, 2007, 1247 pp; *Chem. Abstr.* **2007**, *147*, 9930; (b) Ruminski, P. G.; Clare, M.; Collins, P. W.; Desai, B. N.; Lindmark, R. J.; Rico, J. G.; Rogers, T. E.; Russell, M. A.; et al. PCT Int. Appl. 9 708 145, 1997; *Chem. Abstr.* **1997**, *126*, 264011.
20. Alvarez-Puebla, R. A.; Cui, B.; Bravo-Vasquez, J.-P.; Veres, T.; Fenniri, H. J. *Phys. Chem. C* **2007**, *111*, 6720–6723.
21. (a) Li, S.; Yang, X.; Huang, W. *Macromol. Chem. Phys.* **2005**, *206*, 1967–1972; (b) Beecroft, L.; Ober, C. K. *Chem. Mater.* **1997**, *9*, 1302–1317; (c) Caseri, W. *Macromol. Rapid Commun.* **2000**, *21*, 705–722; (d) Fan, J.; Bozzola, J. J.; Gao, Y. *J. Colloid Interface Sci.* **2002**, *254*, 108–112.
22. Chen, L. S.; Chen, G. J.; Tamborsk, C. J. *J. Organomet. Chem.* **1981**, *215*, 281–291.