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## Sequential Nucleophilic Substitution: A Powerful Strategy for the Solid-Phase Production of Diverse Compound Libraries

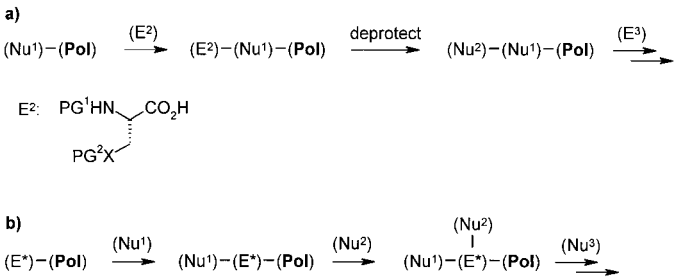
Florencio Zaragoza* and Henrik Stephensen

Solid-phase synthesis enables automated multistep syntheses to be performed in parallel and, therefore, plays an outstanding role in the quest for new candidates for development in the pharmaceutical industry.[1] We report here a new synthetic strategy which is rapid, because a new element of diversity is introduced in each step, and which enables the direct use of unprotected, polyfunctional reagents.

Solid-phase synthetic sequences suitable for library production must be based on reagents available in large number and with a broad variety of additional structural elements. For drug discovery it is important to include structural elements relevant for protein binding (e.g. hydrogen-bond donors and acceptors, cationic, anionic, aromatic, or lipophilic groups).[2] The efficient development of synthetic sequences must be initiated by an evaluation of commercially available reagents and of reactions which can be conducted on insoluble supports. Such an analysis reveals that only a few types of reagent are available in a wide variety for the preparation of diverse compound libraries. The most suitable of these are amines, alcohols, carboxylic acids, and thiols. Reagents with two required reactive groups (amino acids, amino alcohols, haloketones, anthranilic acids, 2-iodophenols, etc.), on the other hand, are not available in large numbers and are, therefore, less suitable for library production.

The evaluation of reactions shows that acylations and other electrophilic transformations of support-bound intermediates will severely limit the choice of additional functional groups present in the final product. Hydrogen-bond donors, for instance, must generally be protected to prevent them from being acylated as well (Scheme 1), but monoprotected bifunctional reagents are expensive and not readily available. On the other hand, nucleophilic transformations of support-bound intermediates do not usually require protection of the additional functional groups, which enables the direct use of unprotected, polyfunctional reagents. Moreover, most of our preferred reagents (see above) are nucleophiles, and we conclude that, for the production of large and diverse arrays of potential drug candidates, nucleophilic substitutions must play a central role. Syntheses which enable repetitive nucleophilic substitutions to be carried out with a support-bound polyelectrophile (Scheme 1) will be most useful.[3]

As an illustrative example of sequential nucleophilic subsitution, we present here a solid-phase synthesis of substituted 2-thio-3-aminopropionic acid derivatives (Scheme 2). We used 2,3-dichloropropionic acid as a polyelectrophile, either esterified with Wang resin (**1a**) or linked to a support-bound amine (**1b**).[4] Treatment of **1** with excess thiol $R^1SH$ in the presence of DIPEA led to a clean, double nucleophilic substitution, yielding the resin-bound 2,3-dithio-




Scheme 1. a) Traditional oligomer (e.g. peptide) synthesis by sequential acylations/deprotections. Side-chain protection is required; few building blocks are available. b) Sequential nucleophilic substitutions on a support-bound polyelectrophile. No side-chain protection is required; many building blocks are available. Nu: nucleophile, E: electrophile, E*: polyelectrophile, Pol: polymeric support, PG: protective group.

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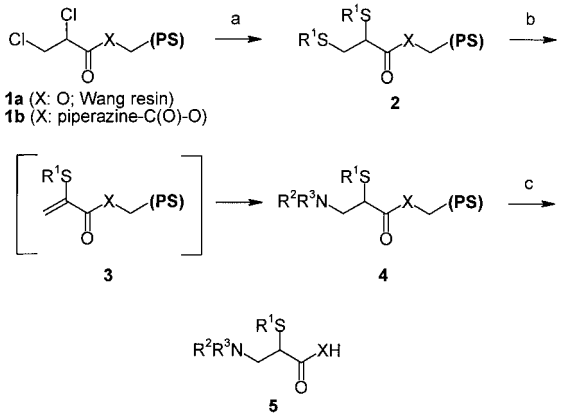


Scheme 2. a) (PS): 1% cross-linked polystyrene with Wang linkages, $R^1$-$R^3$: see Table 1. $R^1SH$, DIPEA, NMP, 20 °C, 1–22 h; b) $R^2R^3NH$, DBU, NMP, 20 °C (X = O or $R^1$ = aryl) or 80 °C (X = NR and $R^1$ = alkyl or $R^2$ = aryl), 22 h; c) TFA/$CH_2Cl_2$ 1/1, 20 °C, 0.5 h. DIPEA = diisopropylethylamine, NMP = 1-methylpyrrolidin-2-one, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TFA = trifluoroacetic acid.

propionic acid derivative **2**.[5] Further treatment of **2** with an amine in the presence of DBU led to $\beta$-elimination of one thiol and incorporation of the amine by a Michael addition.[6]

This new reaction sequence proceeds well with aromatic and aliphatic thiols, although when using aliphatic thiols in combination with the support-bound amide **1b**, heating is generally required to achieve complete incorporation of the amine $R^2R^3NH$. We have used primary and secondary aliphatic amines, $\alpha$-amino acid esters, and aniline with success. Both the thiols and the amines can be polyfunctional (e.g. **5f**, **5g**, **5j**; Table 1), making this synthetic sequence suitable for the production of highly functionalized compounds, without the need for protecting groups.

In conclusion, sequential nucleophilic substitution is a fast and efficient tool for the production of highly diverse compound libraries. Other polyelectrophiles, such as polyhalogenated arenes, have also proved suitable for sequential nucleophilic substitution on solid-phase supports and these results will be reported in due course.

## *Experimental Section*

Synthesis of **5a**-TFA. DIPEA (0.9 mL, 5.17 mmol, 8.6 equiv), and thiophenol (0.6 mL, 5.84 mmol, 10 equiv) were added, in the order given, to a suspension of **1a** (0.60 g, ca. 0.6 mmol) in NMP (9.0 mL). The mixture was shaken at 20 °C for 22 h, filtered, and the resin was washed with NMP (3 × 6 mL). The resin was suspended in NMP (9 mL), and piperidine (0.6 mL, 6.07 mmol, 10 equiv) and DBU (0.9 mL, 6.02 mmol, 10 equiv) were added. The mixture was shaken at 20 °C for 22 h, filtered, and extensively washed with NMP, $CH_2Cl_2$, and methanol. Cleavage from the support was effected by treatment of the resin with TFA/$CH_2Cl_2$ (1/1, 9 mL, 20 °C, 0.5 h). Filtration, and concentration of the filtrate yielded crude **5a** (306 mg, 99% pure by evaporative light scattering) as an oil. Crystallization from AcOEt/heptane at −20 °C yielded the title compound (144 mg, 63%) as a colorless solid; m.p. 81–83 °C; LCMS: *m/z*: 266 [$MH^+$]; $^1$H NMR (400 MHz, [$D_6$]DMSO) $\delta$ = 1.51 (br.s, 2H), 1.72 (br.s, 4H), 2.98–3.29 (m, 4H), 3.34 (dd, $J$ = 13.5 Hz, 1H), 3.53 (dd, $J$ = 13.8 Hz, 1H), 4.29 (dd, $J$ = 5.8 Hz, 1H), 7.38–7.43 (m, 3H), 7.50–7.55 (m, 2H); $^{13}$C NMR (100 MHz, [$D_6$]DMSO) $\delta$ = 20.48 (t), 21.82 (t), 43.41 (d), 52.40 (t), 56.26 (t), 128.21 (d), 128.81 (d), 130.35 (s), 132.45 (d), 170.08 (s); elemental analysis calcd for $C_{14}H_{19}NO_2S \cdot C_2HF_3O_2$ (379.40): C 50.65, H 5.31, N 3.69; found: C 50.94, H 5.38, N 3.63.

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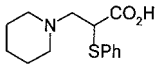
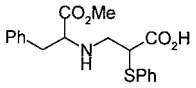
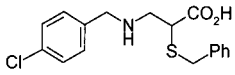
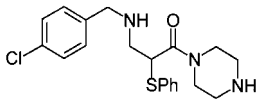
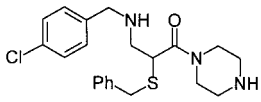
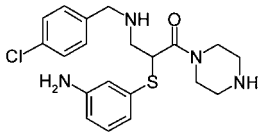
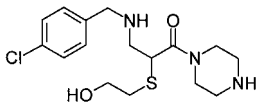
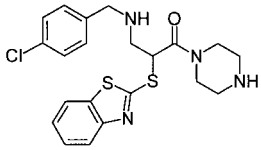
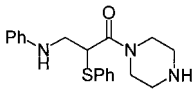
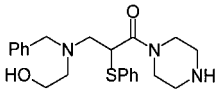
Table 1. Yields and purities of crude 3-amino-2-thiopropionic acid derivatives **5**

| Compound | Product[a] | Purity [%][b] (214 nm/254 nm) | Yield [%][c] |
|---|---|---|---|
| **5a** |  | 90/100 | 75 |
| **5b** |  | 73/85[d] | 49 |
| **5c** |  | 85/–[e] | 75 |
| **5d** |  | 90/95 | 95 |
| **5e** |  | 68/75[d,f] | 73 |
| **5f** |  | 82/86 | 79 |
| **5g** |  | 72/–[e] | 31 |
| **5h** |  | 50/64 | 74 |
| **5i** |  | 61/86[d,f] | 90 |
| **5j** |  | 91/87 | 94 |

[a] All products are TFA salts. [b] The wavelength numbers refer to the HPLC UV detector. [c] Determined by $^1$H NMR spectroscopy using [$D_6$]DMSO as an internal standard and calculated on the basis of a loading of 1.00 mmol g$^{-1}$ in resin **1a** and a loading of 0.68 mmol g$^{-1}$ in resin **1b**.[7] [d] $^1$H NMR spectrum is available as Supporting Information on the WWW or from the author. [e] The product showed no significant absorption at 254 nm. [f] The second nucleophilic substitution was conducted at 80 °C.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[3] The highest possible number of sequential nucleophilic substitutions will depend on the structure of the polyelectrophile chosen. Two or three sequential substitutions with typical nucleophiles will lead to products reaching the highest recommended molecular weight for an orally available drug (ca. 500–600 g mol$^{-1}$).

[4] As a model amine we used piperazine bound to the Wang resin as a carbamate: F. Zaragoza, S. V. Petersen, *Tetrahedron* **1996**, *52*, 10823–10826. Primary amines bound to polystyrene through backbone amide linkages can also be used, which expands the scope of this synthesis significantly.


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[5] The structure of resin **2** was confirmed by acidolytic cleavage from the support and analysis of the crude product by HPLC and LCMS.
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[7] The loading of resin **1a** was as indicated by the manufacturer. The loading of resin **1b** was determined by acylation with 4-fluoro-3-nitrobenzoic acid, cleavage from the support, and yield determination of the monoacylated piperazine by $^1$H NMR spectroscopy.

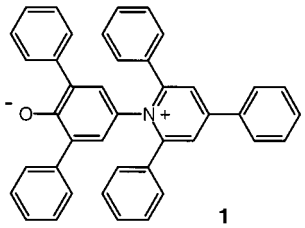
## New Solvatochromic Dyes of the 5-Dimethylamino-5′nitro-2,2′-bithiophene Type**

Horst Hartmann,* Katrin Eckert, and Anke Schröder

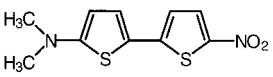
*Dedicated to Professor Christian Reichardt on the occasion of his 65th birthday*

Solvatochromic dyes are suitable as probes for the determination of solvent polarity.[1] Pyridinium betaines **1**, whose long-wavelength absorption is shifted towards shorter wavelengths by more than 9700 cm$^{-1}$ (negative solvatochromism) on changing from a nonpolar to a polar solvent, have proved to be particularly suitable for this purpose.[2] However, probe dyes **1** suffer from the defect that in acidic solvents they can lose their solvent sensitivity in part or totally by protonation. This disadvantage is not displayed by the positive solvatochromic 2,2′-bithiophene dye **2a** described recently by Effenberger and Würthner.[3] It can therefore also be used to advantage for the determination of the solvent polarity of protic solvents. More recently the polarity of solid surfaces was also determined with this dye.[4] However, in comparison to **1**, **2a** exhibits a significantly lower solvent sensitivity of about 4700 cm$^{-1}$, which is only about half the value for the pyridinium betaine dye.

In the synthesis of 5-dimethylamino-5′-nitro-substituted 2,2′-bithiophene **2a**, use was made of a heteroaryl – heteroaryl coupling mediated by organometallic intermediates. This method is also suitable for the preparation of other 5-donor-5′acceptor-substituted 2,2′-bithiophenes.[3] Until now, however, it has not been suitable for the synthesis of compounds of analogous structure in which, for example the thiophene fragment is replaced by ring systems with equal numbers of π electrons. Consequently, nothing is known of the suitability of such compounds for the determination of solvent polarity.



**1**



**2a**

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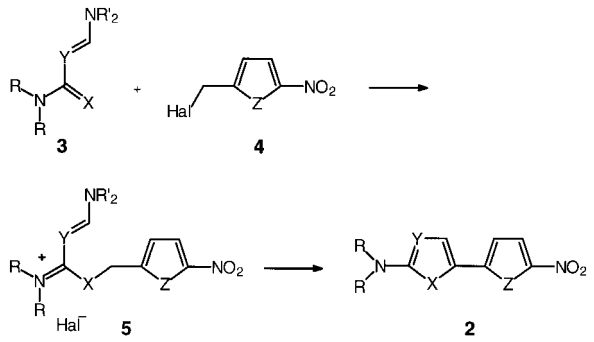

**3** **4** **5** **2**

We describe now an alternative route for the preparation of **2a** that is also suitable for the synthesis of other compounds of structure **2** in which the dimethylamino and the nitro groups may be replaced by other substituents with electron-donor or electron-acceptor properties and the thiophene rings may be replaced by other ring systems of similar electronic structure. The principle features of this route were developed initially by Rajappa in the 1970s[5] and later expanded by, in particular, Liebscher and ourselves. [6] It consists of the reaction of a compound of the general formula **3**[7, 8] with a halomethyl compound **4** with formation of iminium salts of type **5**. These are then transformed into the respective target compounds of type **2** by treatment with a suitable auxiliary base.

Table 1 illustrates a number of the compounds of the general type **2** which we have been prepared. Their structures were confirmed by elemental analysis and by spectrographic methods.[9] Characteristic compound data are summarized in Table 2.

The compounds described are highly crystalline, air-stable but light-sensitive solids. Their color is highly dependent upon

Table 1. Selected compound data of compounds of type **2**.[a,b]

**2b**: M.p. 160 – 162 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.23$ (t, 4H, $NCH_2$), 3.74 (t, 4H, $OCH_2$), 6.28 (d, 1H, CH), 7.09 (d, 1H, CH), 7.45 (d, 1H, CH), 7.97 (d, 1H, CH)

**2c**: M.p. 142 – 143 °C; $^1$H NMR ($CDCl_3$): $\delta = 6.51$ (d, 1H, CH), 6.85 (d, 1H, CH), 7.12 – 7.17 (m, 3H, CH), 7.20 – 7.23 (m, 4H, CH), 7.30 – 7.36 (m, 4H, CH), 7.78 (d, 1H, CH)

**2e**: M.p. 233 – 234 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.51$ (t, 4H, $NCH_2$), 3.79 (t, 4H, $OCH_2$), 7.18 (d, 1H, CH), 7.85 (s, 1H, CH), 8.02 (d, 1H, CH)

**2g**: M.p. 206 – 207 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.04$ (s, 3H, $CH_3$), 5.79 (d, 1H, CH), 6.66 (d, 1H, CH), 7.32 (d, 1H, CH), 7.76 (d, 1H, CH)

**2h**: M.p. 210 – 212 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.20$ (m, 4H, $NCH_2$), 3.85 (m, 4H, $OCH_2$), 6.08 (d, 1H, CH), 6.74 (d, 1H, CH), 7.30 (d, 1H, CH), 7.78 (d, 1H, CH)

**2i**: M.p. 220 – 221 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.04$ (s, 6H, $CH_3$), 5.86 (d, 1H, CH), 7.38 (d, 1H, CH), 7.43 (d, 2H, CH), 8.10 (d, 2H, CH)

**2j**: M.p. 200 – 201 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.21$ (m, 4H, $NCH_2$), 3.85 (m, 4H, $OCH_2$), 6.16 (d, 1H, CH), 7.40 (d, 1H, CH), 7.48 (d, 2H, CH), 8.14 (d, 2H, CH)

**2k**: M.p. 260 – 262 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.54$ (m, 4H, $NCH_2$), 3.82 (m, 4H, $OCH_2$), 6.79 (d, 1H, CH), 7.44 (s, 1H, CH), 7.79 (d, 1H, CH)

**2l**: M.p. 226 – 228 °C; $^1$H NMR ($CDCl_3$): $\delta = 3.83$ (m, 4H, $NCH_2$), 3.81 (m, 4H, $OCH_2$), 7.43 (d, 2H, CH), 7.51 (s, 1H, CH), 8.15 (d, 2H, CH)

**2m**: M.p. 122 – 125 °C; $^1$H NMR ([$D_6$]DMSO): $\delta = 2.95$ (s, 6H, $CH_3$), 5.92 (d, 1H, CH), 7.04 (d, 1H, CH), 7.21 (d, 1H, CH), 7.74 (d, 1H, CH)

**2n**: M.p. 147 – 148 °C; $^1$H NMR ([$D_6$]DMSO): $\delta = 3.17$ (t, 4H, $NCH_2$), 3.74 (t, 4H, $OCH_2$), 6.20 (d, 1H, CH), 7.12 (d, 1H, CH), 7.24 (d, 1H, CH), 7.77 (d, 1H, CH)

[a] For the substitution pattern, see Table 2. [b] **2a**: ref. [3], **2d**: ref. [6d], **2f** and **2o**: ref. [6e], **2p** and **2q**: ref. [11b].

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