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Click chemistry on solid support: synthesis of a new REM resin and application for the preparation of tertiary amines

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Abstract—1,3-Dipolar cycloaddition was employed for the synthesis of a highly practical REM resin. Exploiting this concept, the resulting triazolylmethyl acrylate (TMA) resin was used for an efficient parallel synthesis of tertiary amines by Michael addition, subsequent quarternization and cleavage by means of β-elimination.

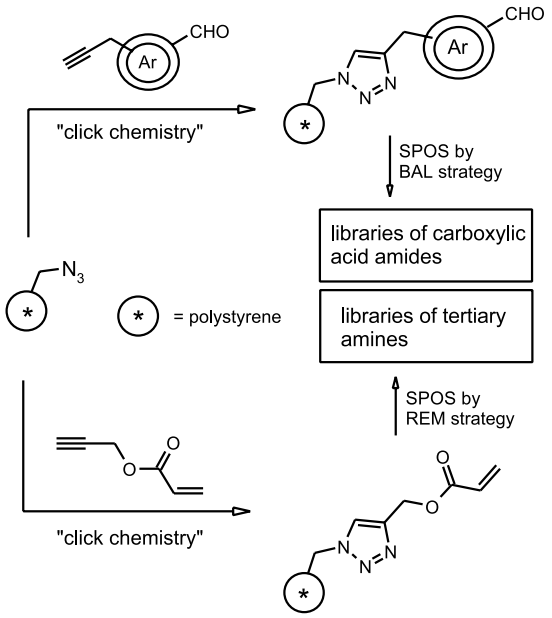
1. Introduction

Solid phase organic synthesis (SPOS) has become an area of huge interest in the field of organic and medicinal chemistry.[1] In contrast to solid phase peptide synthesis (SPPS), the application of SPOS comprises a broad variety of different organic reactions. There is an increasing demand to establish a great number of linking strategies in order to translate reaction types from solution to solid phase.[2] Ideally, the linker should be traceless, recyclable and easily attachable to a polystyrene based backbone. Typically, SPOS handles are connected to aminomethyl substituted polystyrene via a carboxylic function resulting in a secondary amide bearing a free NH that can be crucial for some reaction conditions during the SPO synthesis. On the other hand, linker immobilization by ether formation albeit leading to a widely inert functionality is hard to monitor. Thus, there is still need for the development of new linking strategies.

Very recently, we reported on the construction and application of a new family of backbone amide linkers (BAL) that were accessible by 1,3-dipolar cycloaddition of azidomethyl polystyrene and a propargyl or propargyloxy substituted arene carbaldehyde (Scheme 1) when the triazole formation was high yielding and conveniently monitored by IR spectroscopy.[3]

The resulting click linkers were applied for the parallel synthesis of dopaminergic carboxamides. As we were convinced that this click chemistry strategy[4,5] is suitable for the immobilization of a variety a different SPOS handles, we intended to exploit the methodology for the construction of further linkers.

Recently, J. R. Morphy and co-workers introduced the new acrylate- and vinylsulfone-based linkers **1** and **2**, which are in fact regenerative Michael acceptors (REM) being useful for the efficient synthesis of tertiary amines.[6–8] At this, addition of a secondary amine followed by quarternization of the resulting Michael product and subsequent cleavage led to the desired tertiary amines. Following this REM



Scheme 1. Synthesis and application of click chemistry derived BAL and REM resins.

Keywords: Click chemistry; REM Resin; 1,3-Dipolar cycloaddition; SPOS.
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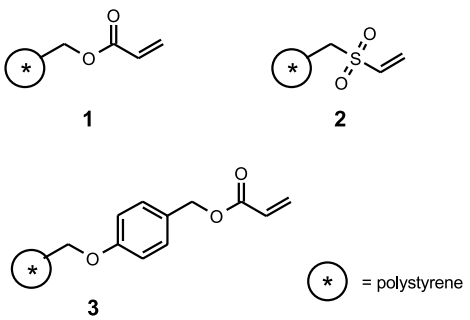
strategy, the acrylate **1** and the Wang resin based analog **3** were applied for the synthesis of δ-opioid receptor ligands,[9] β-peptoides,[10] potential I_f channel blockers[11] and Gly T2 transporter ligands (Scheme 2).[12]

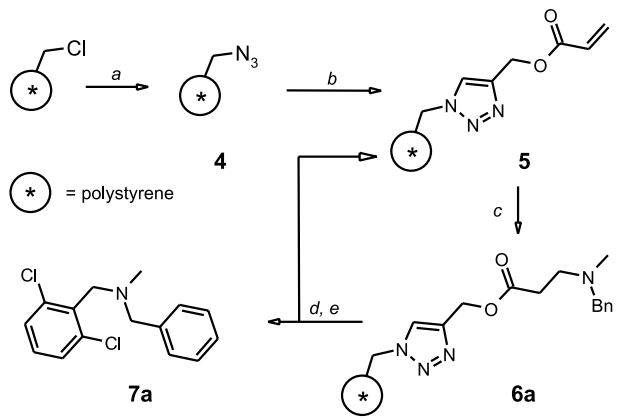


Scheme 2. Commercially available REM resins.

2. Results and discussion

In conjunction with our efforts in the discovery of highly selective dopamine receptor modulators, we are especially interested in tertiary amines being known as a valuable pharmacophoric functions. Thus, we decided to choose a REM based methodology for the extension of our studies on the application of click chemistry for the immobilization of linking units. In detail, we started from azidomethyl substituted polystyrene **4**, which was easily prepared by nucleophilic substitution of Merrifield resin with NaN_3.[13] The subsequent 1,3-dipolar cycloaddition with commercially available propargyl acrylate[14] was conducted in DMF/THF in the presence of DIPEA and catalytic amounts of Cu(I)I leading to the triazolylmethyl acrylate (TMA) resin **5** (Scheme 3). Addition of benzylmethylamine proceeded smoothly in DMF at room temperature. Subsequent alkylation of the aminopropionate **6a** with 2,6-dichlorobenzyl bromide was followed by base induced cleavage leading to the tertiary amine **7a** in 68% yield based on the loading of **5**. ^{1}H NMR analysis of the final product indicated a purity >95%. It is worthy of note that the use of a regenerated resin **5** for another identical reaction cycle resulted in the formation of **7a** in almost equal yield (66%).

Figure 1 documents a diagnostic IR analysis when both the azido and the ester C═O functionality reveal strong



Scheme 3. (a) NaN_3, DMSO, 70 °C, 48 h; (b) propargyl acrylate, Cu(I)I, DMF, THF, DIPEA, 35 °C, 10 h; (c) benzylmethylamine, DMF, rt, 16 h; (d) 2,6-dichlorobenzyl bromide, DMSO, rt, 16 h; (e) TEA, DMF, rt, 16 h.

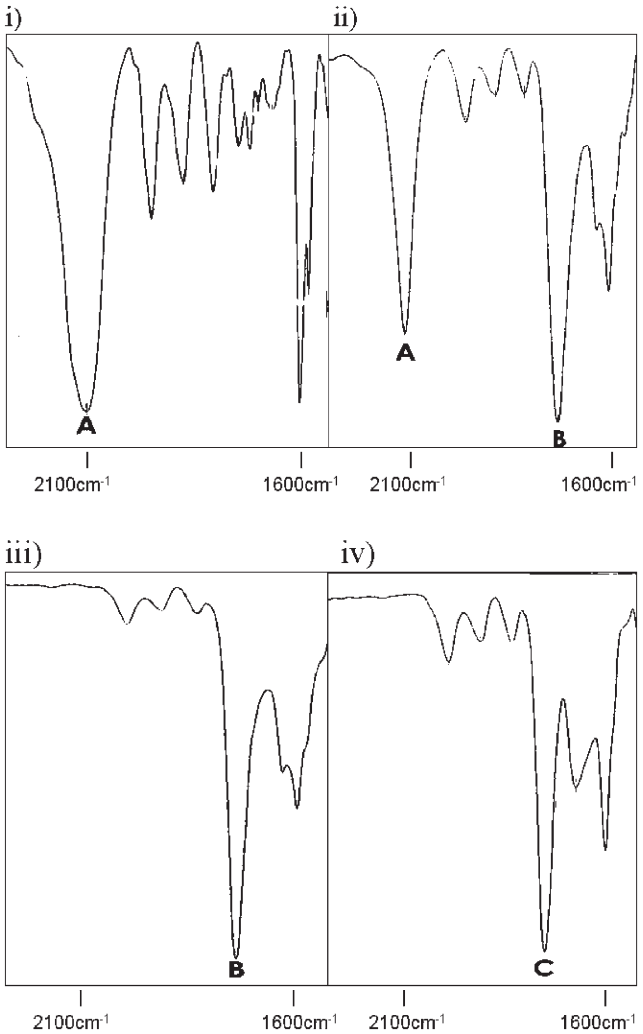


Figure 1. IR monitoring of solid phase reactions. All spectra range from 2300 to 1500 cm^{-1}. (i) Resin **4** with azido band at 2096 cm^{-1} (**A**); (ii) sample after 5 h reaction time of **4** with propargyl acrylate still showing an azido band at 2096 cm^{-1} (**A**) and a signal for the acrylic ester moiety at 1732 cm^{-1} (**B**); (iii) sample after 10 h reaction time of **4** with propargyl acrylate displaying the acrylic ester signal at 1732 cm^{-1} (**B**) and complete disappearance of the azido group; (iv) resin **6a** with a slightly shifted ester signal at 1735 cm^{-1} (**C**).

IR absorption. The progression of the cycloaddition can be monitored conveniently and precisely. After 5 h of reaction time, the signal of the azido group (2096 cm^{-1}) has been distinctly shrunk whereas a carbonyl band (1732 cm^{-1}) becomes visible. Another 5 h of reaction time leads to a complete disappearance of the N_3-signal. The 1,4-addition of an amine results to a slight shift the carbonyl band, whereas the E1cb elimination regenerated the acrylate resin showing IR absorption at 1732 cm^{-1} (not shown).

In order to evaluate our new TMA resin and to compare it to the off-the-shelf REM support **1**, we accomplished a parallel synthesis of six tertiary amines. In detail, the Michael acceptor **5** was treated with tetrahydroisochinoline or phenylpiperazine to give the Michael products **6b** and **6c**, respectively. Subsequent alkylation with allyl bromide, *p*-nitrobenzyl bromide or methyl bromoacetate followed by Hofmann elimination gave the tertiary amines **7b–f**, respectively.

Employing phenylpiperazine as a secondary amine and methyl bromoacetate an electrophile, the reaction led to the 4-bromophenylpiperazine **8** when LCMS indicated a product of high purity and the mass signals of m/z=313 ($M+1^+$) and 315 ($M+3^+$) revealed the typical isotope pattern of bromine. ^{1}H NMR spectra indicated an AA'BB' coupling pattern for the protons of the phenyl moiety. Being known that 2-haloacetonitriles can act as efficient halogenating reagents,[15] we assume that the excess of bromoacetate reacted analogously, in this case.

For all SPOS products investigated, the yields were satisfying and comparable to those described in the literature based on resin **1** (Table 1). LCMS analysis employing reversed phase chromatography in combination with UV (220 nm) and ESI-ion trap detection indicated excellent purities (>92%).

In conclusion, a convenient and practical construction of a triazolylmethyl acrylate (TMA) resin employing 1,3-dipolar cycloaddition as the key immobilization step facilitates an efficient parallel synthesis of differently substituted tertiary amines. Application for a combinatorial approach to selective dopamine receptor modulators is currently in progress.

3. Experimental

3.1. General

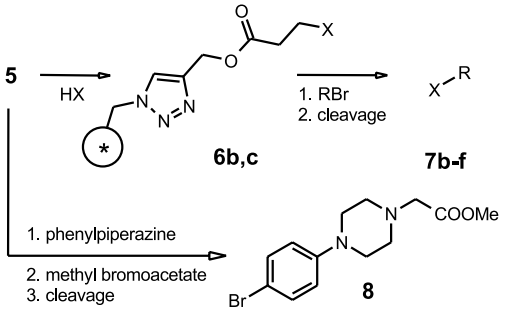
Solvents and reagents were purified and dried by standard procedures or purchased in pure, dry quality from Fluka or Sigma-Aldrich. All reactions were performed under nitrogen atmosphere in a Synthesis 1 synthesizer (Heidolph Instruments) equipped with PFA reaction vessels. LCMS analyses were done with a Bruker Esquire2000 using ESI in positive mode. ^{1}H NMR spectra were recorded on a Bruker AM 360 (360 MHz) spectrometer. IR spectra were recorded on a Jasco FT/IR 410 spectrometer. Micro analyses were performed by Beetz, Mikroanalytisches Laboratorium, Kronach, Germany.

3.1.1. Azidomethyl polystyrene (4).[13] Merrifield resin (1.0 g, 2.0 mmol/g) was agitated in a PFA vessel with NaN_3 (0.65 g, 10 mmol) in DMSO (10 mL) at 70 °C for 48 h. After being cooled to room temperature, the suspension was filtered through the vessel frit and the resin was rinsed alternately with MeOH (5×20 mL) and CH_2Cl_2 (5×20 mL) and dried in vacuo to give **4** as a colorless resin. FTIR (KBr-pellet) 2096 cm^{-1}.

3.1.2. Triazolymethyl acrylate (TMA) resin (5). Azidomethyl polystyrene (**4**) was agitated in a PFA vessel with proparyl acrylate[14] (1.1 g; 10 mmol), CuI (7.6 mg; 0.04 mmol) DIPEA (1.0 mL, 7.7 mmol) in DMF (4 mL) and THF (4 mL) at 35 °C. The progression of the reaction was monitored by IR spectroscopy. After disappearance of the signal at 2096 cm^{-1}, the suspension was filtered through the vessel frit and the resin was rinsed alternately with pyridine (5×20 mL), MeOH (5×20 mL) and CH_2Cl_2 (5×20 mL) and dried in vacuo to give **5** as a light brown resin. Combustion analysis of nitrogen indicated a loading of 1.63 mmol/g.

3.1.3. Benzyl-(2,6-dichlorobenzyl)-methylamine (7a). TMA resin (**5**) (100 mg) was agitated with benzylmethylamine (200 mg, 1.65 mmol) in DMF (2 mL) for 16 h at ambient temperature. The suspension was filtered through the vessel frit and the resin was rinsed alternately with MeOH (5×5 mL) and CH_2Cl_2 (5×5 mL) and dried in vacuo. The resulting resin **6a** was treated with a solution of 2,6-dichlorobenzyl bromide (200 mg, 0.83 mmol) in DMSO (4 mL) and agitated for 16 h at ambient temperature. After being filtered, the resin was washed with MeOH (3×5 mL) and CH_2Cl_2 (3×5 mL) and TEA (0.2 mL, 14 mmol) in DMF

Table 1. Parallel synthesis using TMA resin



Compound	HX=	R=	Yield[a] (%) (purity, %)[b]	Ref.[6] yield (%) (purity, %)
7b	Tetrahydro-isochinoline	Allyl	82 (95)	88 (>90)
7c	Tetrahydro-isochinoline	*p*-Nitrobenzyl	77 (92)	63 (>90)
7d	Tetrahydro-isochinoline	CH_2CO_2Me	75 (92)	73[c] (>90)
7e	N-Phenyl-piperazine	Allyl	79 (93)	75 (>90)
7f	N-Phenyl-piperazine	*p*-Nitrobenzyl	53 (91)	47 (>90)
8	N-Phenyl-piperazine	CH_2CO_2Me	62[d] (96)	—

[a] Calculated on the loading of **5** (1.63 mmol/g).
[b] Determined by LCMS using MeOH/aq. 0.1 N HCO_2H gradient system on RP-18 material and ESI-ion trap mass spectrometry.
[c] Results for ethyl ester derivative.
[d] Yield of the brominated phenylpiperazine **8**.

(2 mL) was added. Stirring at ambient temperature for 6 h was followed by filtration of the solvent, whereas the resin was washed with DMF (2 mL) and CH_2Cl_2 (3×5 mL). The combined filtrates were washed with a saturated solution of $NaHCO_3$ and evaporated to dryness to give 32 mg (68%) of **7a** as a colorless solid. ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm)=2.18 (s, 3H), 3.62 (s, 2H), 3.84 (s, 2H), 7.13 (t, 1H), 7.21–7.36 (m, 7H); ESI-MS (*m*/*z*) 276 ($M+1^+$).

3.1.4. Parallel synthesis of tertiary amines (7b–f) and (8). Tertiary amines **7b–f** and **8** were synthesized following the procedure described for **7a** starting in each case from 100 mg of **5**. Yields are given in Table 1. Compounds were characterized by LCMS analysis using Agilent Zorbax Eclipse© XDB-C8 (5 μm) and MeOH/0.1 N aq. formic acid gradient system (50:50 to 95/5) in combination with ES ionization and ion trap detection in positive mode and by ^{1}H NMR as follows.

N-Allyl-1,2,3,4-tetrahydroisochinoline (**7b**). ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm)=2.75 (t, 2H), 2.91 (t, 2H), 3.18 (d, 2H), 3.63 (s, 2H), 5.19 (d, 1H), 5.26 (d, 1H), 5.90–6.01 (m, 1H), 6.99–7.13 (m, 4H); ESI-MS (*m*/*z*) 203 ($M+1^+$).

2-(4-Nitrobenzyl)-1,2,3,4-tetrahydroisochinoline (**7c**). ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm)=2.77 (t, 2H), 2.92 (t, 2H), 3.65 (s, 2H), 3.78 (s, 2H), 6.96–7.15 (m, 4H), 7.56–7.61 (m, 2H), 8.17–8.21 (m, 2H); ESI-MS (*m*/*z*) 269 ($M+1^+$).

Methyl-(1,2,3,4-tetrahydroisochinolin-2-yl)-acetate (**7d**). ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm)=2.87–2.97 (m, 4H), 3.43 (s, 2H), 3.75 (s, 3H), 3.80 (s, 2H), 6.98–7.14 (m, 4H); ESI-MS (*m*/*z*) 206 ($M+1^+$).

1-Allyl-4-phenylpiperazine (**7e**). ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm)=2.59–2.63 (m, 4H), 3.06, (d, 2H), 3.19–3.23 (m, 4H), 5.15–5.26 (m, 2H), 5.84–5.96 (m, 1H), 6.82–6.94 (m, 3H), 7.22–7.28 (m, 2H); ESI-MS (*m*/*z*) 203 ($M+1^+$).

1-(4-Nitrobenzyl)-4-phenylpiperazine (**7f**). ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm)=2.60–2.65 (m, 4H), 3.19–3.24 (m, 4H), 3.66 (s, 2H), 6.84–6.95 (m, 3H), 7.24–7.29 (m, 2H), 7.53–7.57 (m, 2H), 8.17–8.22 (m, 2H); ESI-MS (*m*/*z*) 298 ($M+1^+$).

Methyl (4-(4-bromophenyl)-piperazin-1-yl)-acetate (**8**). ^{1}H NMR ($CDCl_3$, 360 MHz): δ (ppm)=2.73 (t, 4H), 3.21 (t, 4H), 3.29 (s, 2H), 3.74 (s, 3H), 6.76–6.81 (m, 2H), 7.31–7.36 (m, 2H); ESI-MS (*m*/*z*) 313, 315 ($M+1^+$).

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