Multicomponent Reactions as a Powerful Tool for Generic Drug Synthesis

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Abstract: Multicomponent reactions (MCRs) are not only a powerful tool for drug discovery, they also represent an excellent methodology for synthesis rationalization. Here we wish to illustrate the potential of MCRs in the production of generic drugs by synthesizing, in racemic form, the antiplatelet agent clopidogrel and the non-steroidal antiandrogen bicalutamide, using Ugi, Petasis and Passe-rini reactions.

Key words: multicomponent reactions, drugs, cleavage, clopido-grel, bicalutamide

Multicomponent reactions (MCRs) are not only a powerful tool for the creation of chemical diversity and new chemical entities in drug discovery, 1,2 they also represent an excellent methodology for synthesis rationalization, 3 for example, in the production of generic drugs or natural products. 4 In order to demonstrate the potential of multi-component chemistry, we herein report alternative, MCR-based synthetic approaches to the well-known drugs, (S)-clopidogrel (1) and bicalutamide (2) (Figure 1).

First, we report the racemic synthesis of the antiplatelet agent (S)-methyl-α-5-(4,5,6,7-tetrahydro[3,2-c]thienopyr-idyl)-(2-chlorophenyl)acetate (clopidogrel; 1), 5 the world’s second-highest-selling pharmaceutical in 2005 (Plavix®), via an Ugi three-component reaction. The bioactive compound can be regarded as an ester of a non-natural α-amino acid and is therefore accessible by different synthetic routes based on MCR chemistry. A three-component Ugi reaction with cleavable isocyanides (methods A/C) and a Petasis reaction (method B) with suitable starting materials, were improved to synthesize the carboxylic acid 3, a precursor of racemic (R,S)-clopidogrel (4; Scheme 1). The Ugi reaction (U-3CR) 6 involves the 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (5), which is commercially available as the corresponding hydrochloric acid salt, 2-chlorobenzaldehyde (6) and 1-isocyanocyclohexene (Armstrong isocyanide; 7) as acid-labile cleavable isocyanide. 7 The reaction was performed in methanol under microwave irradiation and formic acid catalysis. The Ugi product 8 was obtained in excellent yield after one hour at 60 °C.

Subsequent cleavage of the isocyanide moiety with aqueous hydrochloric acid allowed fast and complete conversion of 8 into the desired carboxylic acid 3. An alternative, one-step synthetic route to the precursor 3 was carried out using the Petasis reaction, which was discovered by Petasis et al. in 1993. 8 This reaction can be regarded as a boronic acid version of the Mannich reaction. In a further optimization protocol, its practical use for the synthesis of non-natural α-amino acids from alkenyl boronic acids and glyoxylic acid has been reported. 9 Thus, we employed compound 5, glyoxylic acid (9) and 2-chlorophenylboronic acid (10) in a Petasis three-component reaction (Petasis-3CR). Solvent optimization showed that using DMF allowed acceptable yields for the formation of carboxylic acid 3. After obtaining the precursor 3 by these two different methods, a final esterification step yielded the desired racemic clopidogrel 4 with high conversion and high purity (>99%). Although method B enabled a reduction in the number of the reaction steps, method A presented a very efficient and promising three-step synthesis of racemic (R,S)-clopidogrel (4).

In our efforts to optimize the synthetic strategy, we investigated the use of a base-labile isocyanide – 1,1-dimethyl-2-isocyanoethyl methyl carbonate (11) – in the U-3CR (Scheme 2, method C). This isocyanide, reported by Lindhorst and co-workers, 10 allowed the direct formation of racemic clopidogrel from the Ugi-product 12. The Ugi reaction was performed at 60 °C under microwave irradiation in the presence of an equimolar amount of formic acid, followed by the cleavage of the isocyanide moiety by treatment with potassium tert-butoxide in tetrahydrofuran. This synthetic route allowed the formation of (R,S)-clopidogrel (4) with moderate yields; the lower yields being due to the instability of the carbamate moiety of the isocyanide 11, which is partially hydrolyzed during the reaction sequence.

In conclusion, we demonstrate that three new synthetic methods, based on MCR chemistry, give easy synthetic access to (R,S)-clopidogrel (4). Scheme 3 summarizes these methods and compares them with the original synthesis patented by Sanofi. 11 Even though method A involves three synthetic steps, the route gives the best overall yield and illustrates the efficiency of MCR chem-
Scheme 1  Synthesis of (R,S)-clopidogrel (4) via U-3CR with Armstrong isocyanide (method A) or Petasis-3CR (method B) followed by esterification

Scheme 2  Two-step U-3CR synthesis of (R,S)-clopidogrel (4) using the Lindhorst isocyanide (method C)

Scheme 3  New multicomponent syntheses of (R,S)-clopidogrel (4) with respective overall yields
It has been shown that in the titanium tetrachloride assisted Passerini reaction the isocyanide forms an adduct with the titanium tetrachloride. Depending on the structural properties of the isocyanide, either a 1:1 or 1:2 molar ratio is found. The adduct then reacts with the carbonyl compound and, upon hydrolysis of the reaction mixture, an α-hydroxy amide 22 is formed. For the exact mechanism of the titanium tetrachloride assisted Passerini reaction, different models have been discussed and investigated by X-ray diffraction studies. These studies agree on the formation of a titanium-coordinated intermediate 21 with a reactive chloroimide C–Cl bond, which is then hydrolyzed to the α-hydroxy amide 22 (Scheme 5). For our objective, the titanium tetrachloride assisted Passerini reaction is a very attractive method since it leads directly to the α-hydroxy amide moiety of bicalutamide without the need for an additional ester cleavage step. A similar procedure using trifluoroacetic acid (TFA) instead of titanium tetrachloride has been reported; however, this approach proved unsuccessful for the bicalutamide system in pilot experiments.

Several methods for the synthesis of bicalutamide have been reported in the patent literature and scientific publications. Rather advanced processes include the synthesis of enantiomerically pure (R)- and (S)-bicalutamide employing naturally occurring chiral starting materials and a two-step synthesis via 1,2-addition of a methyl sulfone to a keto amide. Our MCR synthesis produces racemic bicalutamide 16 from commercially available starting materials in a two-step process with an overall yield of 61%. 1-(4-Fluorophenylsulfonyl)propan-2-one (14) was prepared by oxidation of 4-fluorophenylthioacetone (13) with 3-chloroperoxybenzoic acid (MCPBA); the reaction proceeded smoothly with a yield of 92%. The 4-cyano-3-(trifluoromethyl)phenylisocyamine (15) can be prepared from the corresponding aniline following known procedures and is commercially available.
For the titanium tetrachloride assisted Passerini reaction, all glassware and solvents were dried carefully, as traces of water drastically reduced the yield. The reaction had to be performed under inert gas atmosphere. In a first step, the isocyanide was combined with titanium tetrachloride to form the initial adduct; the carbonyl component was then added. Upon completion of the conversion, the reaction mixture was quenched with water and an extractive work up followed by recrystallization yielded racemic bicatalumide with a yield of 66% and >99% purity.

In conclusion, we have demonstrated that multicomponent reactions can be a powerful tool for the generic synthesis of marketed drugs. (R,S)-Clopodigrel can be synthesized via Ugi or Petasis reactions in two steps with acceptable to high yields. Furthermore, a short and efficient, two-step synthesis of the anticancer drug (R,S)-bicatalumide via a titanium tetrachloride assisted Passerini reaction has been developed.

1H NMR and 13C NMR spectra were measured in CDCl3 or DMSO-d6 with a Bruker AV 250 spectrometer. Chemical shifts are expressed in ppm (δ) with respect to TMS as an internal standard. Electrospary ionization mass spectra (ESI) were obtained using a Varian LC Prostar 325 system [Varian Polaris RP C18 column; 3 mm x 150 mm; 5 μm ODS A; 215 nm and 254 nm; 1 mL/min, 3 min gradient from 90% H2O to 10% H2O (0.5% HCOOH) vs. MeCN (0.5% HCOOH)]. All starting materials used are commercially available. Isocyanides 7 and 15 are available from Priaux AG. Compound 14 is now commercially available from Otava.

2-(2-Chlorophenyl)-N-cyclohex-2-enyl-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetamide (8)

To a solution of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (5; 100 mg, 0.57 mmol) in MeOH (0.5 mL) was added Et3N (58 mg, 0.57 mmol). The mixture was stirred at r.t. for 5 min, then 2-chlorobenzaldehyde (6; 80 mg, 0.57 mmol) was added and the solution was again stirred at r.t. for 1 h. Formic acid (26 mg, 0.57 mmol) in MeOH (1 mL) was added dropwise, followed by addition of 1-isocyanocyclohexene (7; 61 mg, 0.57 mmol). The mixture was stirred at 60 °C under microwave irradiation for 1 h. Subsequently, the crude reaction mixture was diluted with CH2Cl2 (20 mL), washed with brine (10 mL) and the aqueous layer was extracted with CH2Cl2 (2 x 10 mL). The combined organic layer was dried over MgSO4, evaporated to dryness and purified on a silica gel column (EtOAc–hexane, 1:3) to give 8.

Yield: 92 mg (83%); white solid.

[49x256]×

Electrospray ionization mass spectra (ESI) were obtained using a Varian LC Prostar 325 system [Varian Polaris RP C18 column; 3 mm x 150 mm; 5 μm ODS A; 215 nm and 254 nm; 1 mL/min, 3 min gradient from 90% H2O to 10% H2O (0.5% HCOOH) vs. MeCN (0.5% HCOOH)].

2-(2-Chlorophenyl)-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetic Acid (3) from 8

Compound 8 (60 mg, 0.15 mmol) was dissolved in a mixture THF–HClaq[9:1 (v/v), 1 mL] and the resulting solution was allowed to stir at r.t. for 1 h. The reaction mixture was then diluted with CH2Cl2 (20 mL), washed with brine (10 mL) and the aqueous layer was extracted with CH2Cl2 (2 x 10 mL). The aqueous layer was made basic with sat. NaHCO3 (~0.5 mL) until pH 8, and extracted with CH2Cl2 (2 x 10 mL). The combined organic layer was dried over MgSO4, evaporated to dryness, and the product was crystallized (EtOAc–hexane) to give 3.

Yield: 47 mg (98%); white solid.

[49x256]×

1H NMR (CDCl3, 250 MHz): δ = 7.54 (s, 1 H), 7.45–7.41 (m, 1 H), 7.32–7.23 (m, 2 H), 7.08 (d, J = 5.0 Hz, 1 H), 6.66 (d, J = 5.0 Hz, 1 H), 4.94 (s, 1 H), 3.65 (dd, J = 7.9 Hz, J = 14.4 Hz, 2 H).

13C NMR (CDCl3, 63 MHz): δ = 173.0, 135.4, 132.9, 130.4, 129.6, 127.1, 125.2, 123.2, 69.0, 50.8, 49.1, 25.7.


2-(2-Chlorophenyl)-6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetic Acid (3) to a solution of glyoxyllic acid monohydrate (9; 30 mg, 0.33 mmol) in DME (1 mL) was added 4,5,6,7-tetrahydrothieno[3,2-c]pyridine (8; 46 mg, 0.33 mmol) and 2-chlorophenylboronic acid (10; 51 mg, 0.33 mmol). The reaction mixture was stirred at r.t. for one week. After completion, the crude mixture was evaporated to dryness then dissolved in EtOAc (20 mL) and washed with distilled H2O (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layer was dried over MgSO4, evaporated to dryness and purified on a silica gel column (EtOAc–MeOH, 1:1) to give 3 as a white solid (50 mg, 49%). Analytical data was in accordance with those obtained in the synthesis from 8.

(R,S)-Clopodigrel (4) from 3

To a solution of 3 (20.0 mg, 0.065 mmol) in MeOH (2 mL) was added concd H2SO4 (0.065 mmol). The mixture was refluxed for 3 d (HPLC analysis showed complete conversion into the corresponding methyl ester). The crude product was evaporated to dryness and dissolved in CH2Cl2 (10 mL). The organic layer was washed with sat. NaHCO3 (5 mL), dried over MgSO4 and evaporated to yield 4.

Yield: 18.8 mg (90%); colorless oil.

1H NMR (CDCl3, 250 MHz): δ = 7.72–7.68 (m, 1 H), 7.42–7.30 (m, 1 H), 7.29–7.25 (m, 2 H), 7.05 (d, J = 5.0 Hz, 1 H), 6.66 (d, J = 5.2 Hz, 1 H), 4.92 (s, 1 H), 3.79–3.59 (m, 2 H), 2.88 (s, 4 H). Data are in accordance with those previously published.11

2-(2-(2-Chlorophenyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyridin-5-yl)acetylamino)-1,1-dimethylmethyl Methyl Carbonate (12)

To a solution of 4,5,6,7-tetrahydrothieno[3,2-c]pyridine hydrochloride (5; 100 mg, 0.57 mmol) in MeOH (0.5 mL) was added Et3N (58 mg, 0.57 mmol), and the mixture was stirred at r.t. for 5 min. 2-Chlorobenzaldehyde (6; 80 mg, 0.57 mmol) was added and the solution was again stirred at r.t. for 1 h. Formic acid (26 mg, 0.57 mmol) in MeOH (1 mL) was added dropwise followed by addition of 1,1-dimethyl-2-isocyanoethyl methyl carbamate (11; 90 mg, 0.57 mmol). The mixture was stirred at 60 °C under microwave irradiation for 1 h. Subsequently, the crude reaction mixture was diluted with CH2Cl2 (20 mL) and washed with brine (10 mL). The obtained aqueous layer was extracted with CH2Cl2 (2 x 10 mL) and the combined organic layers were dried over MgSO4, evaporated to dryness and purified on a silica gel column (EtOAc–hexane, 1:4→1:1) to give 12.
Yield: 134 mg (54%); colorless oil.

1H NMR (CDCl₃, 250 MHz): δ = 7.68 (t, 3J = 6.0 Hz, 1 H), 7.45–7.39 (m, 2 H), 7.29–7.21 (m, 2 H), 7.06 (d, 3J = 5.2 Hz, 1 H), 6.65 (d, 3J = 5.1 Hz, 1 H), 4.9 (s, 1 H), 3.74 (s, 3 H), 3.66–3.46 (m, 4 H), 2.89 (s, 1 H), 1.45 (s, 6 H).

13C NMR (CDCl₃, 63 MHz): δ = 170.9, 154.0, 135.3, 133.5, 133.4, 133.1, 130.3, 130.9, 123.9, 126.9, 125.2, 122.9, 83.35, 69.4, 54.2, 50.8, 49.3, 47.5, 25.7, 23.6.

MS (+ESI): m/z = 437 [M + H]⁺.

IR: 3350, 2952, 2844, 1743, 1680, 1514, 1471, 1439, 1278, 1148 cm⁻¹.

(RS)-Clopidoogrel (4) from 12
To a solution of 12 (134 mg, 0.3 mmol) in anhydrous THF (2 mL), was added t-BuOK (44 mg, 0.39 mmol). The resulting suspension was stirred at r.t. for 1 h. The crude reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with H₂O (10 mL). The aqueous layer was stirred at r.t. for 1 h. The crude reaction mixture was diluted was added, (a precipitate was formed) and the resulting suspension was recrystallized (EtOAc–hexane, 1:1) to give 4 as a colorless oil (41 mg, 42%). Analytical data were in accordance with those previously published.18

References
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