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 Passerini reactions.

Key words: multicomponent reactions, drugs, cleavage, clopidogrel, 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 multicomponent 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*]thienopyridyl)-(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**).

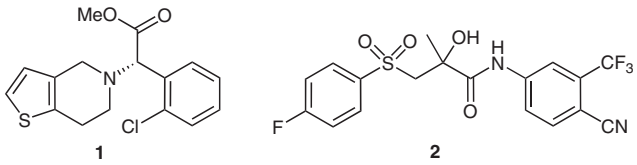

Figure 1 Structures of (*S*)-clopidogrel (**1**) and bicalutamide (**2**)

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-

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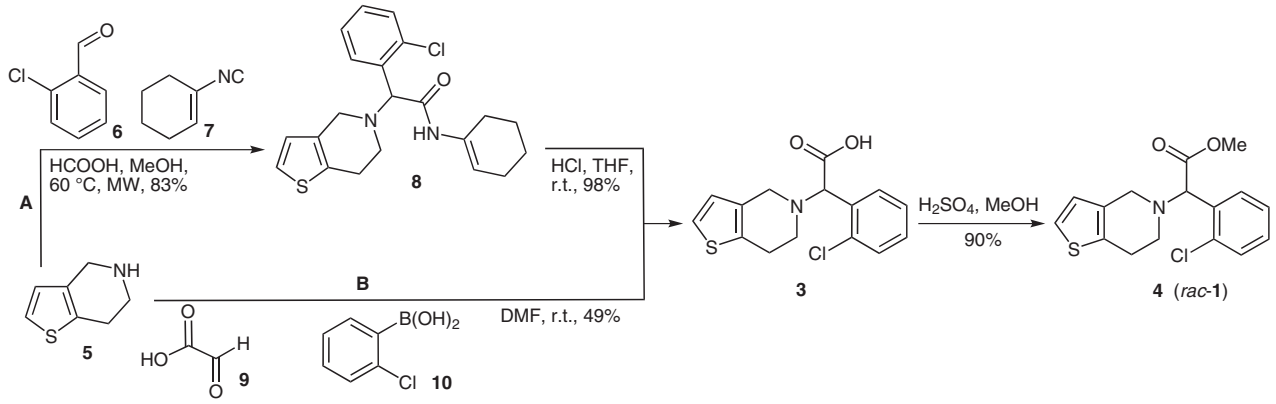
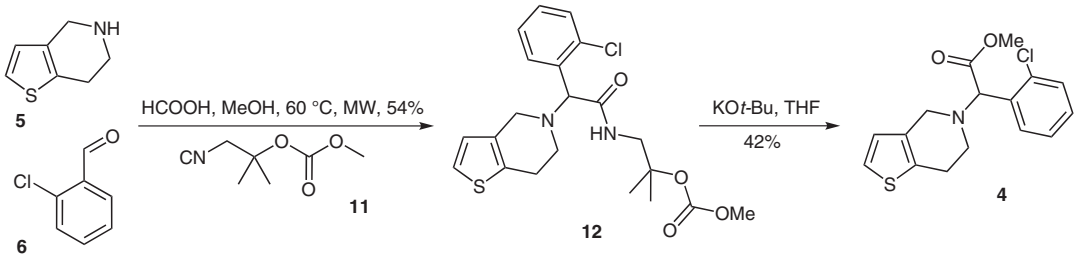
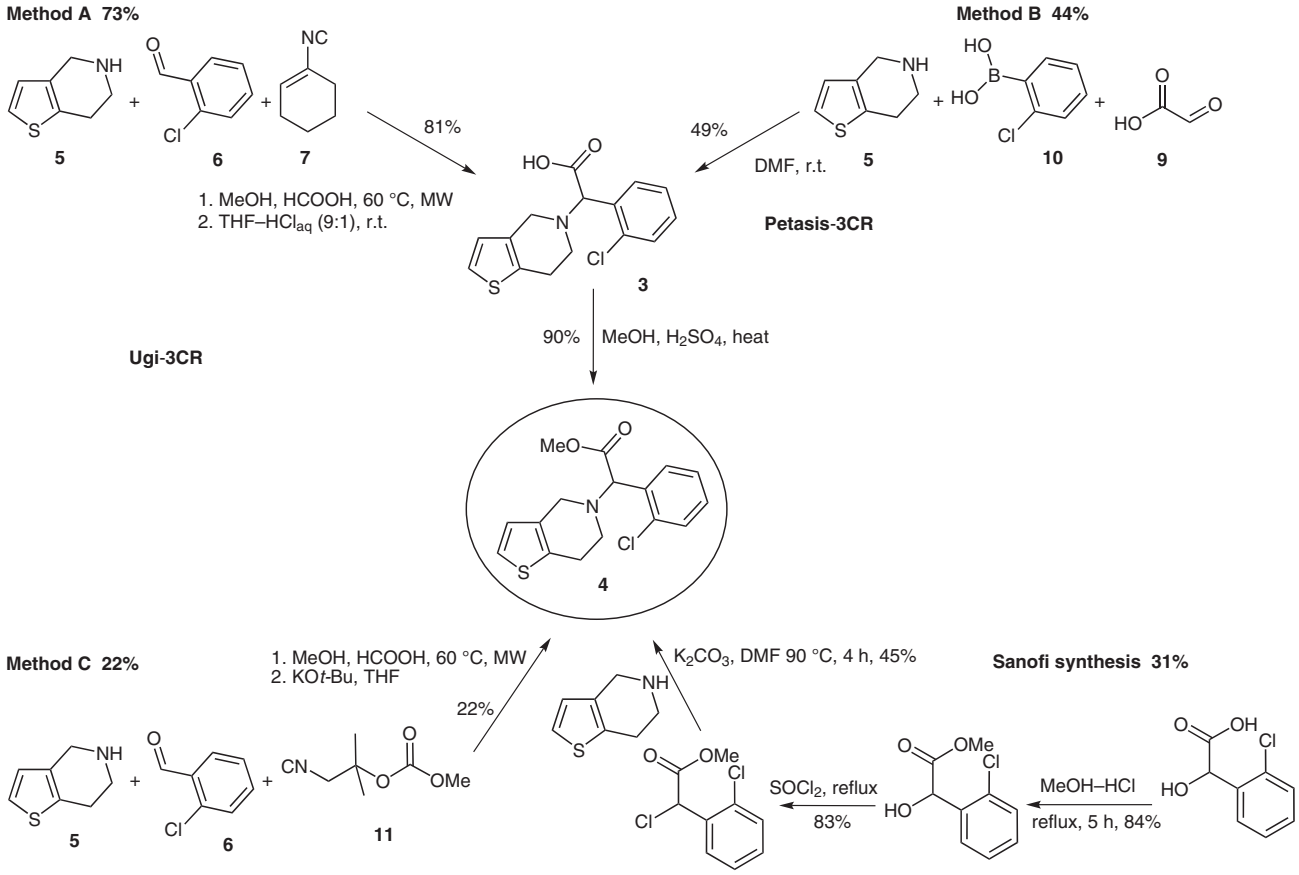


Scheme 1 Synthesis of (*R*,*S*)-clopidogrel (**4**) via U-3CR with Armstrong isocyanide (method A) or Petasis-3CR (method B) followed by esterification



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



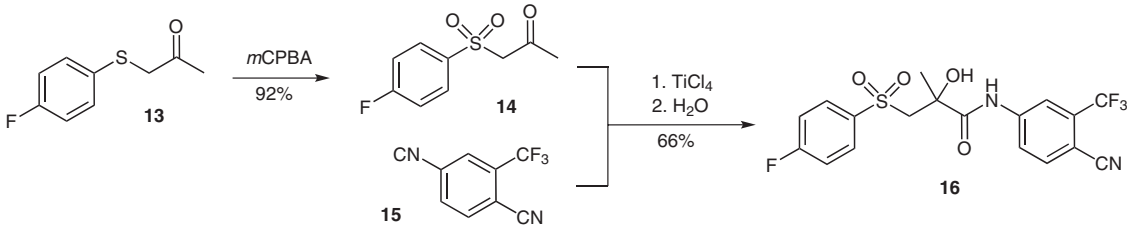
Scheme 3 New multicomponent syntheses of (*R*,*S*)-clopidogrel (**4**) with respective overall yields

istry. Method B also has some advantages such as an acceptable overall yield and a two-step strategy, however, the starting materials are less suitable for scale-up. Method C is not convenient because of its low yield and the instability of the starting material. Therefore, method A definitively represents the best synthetic route that we have developed. The Armstrong isocyanide is easily synthesized in up to kilogram scales in two steps; it can be stored at –20 °C. The only hindrance for its use arises through is its piercing odor. Alternatively, new, cleavable isocyanides with promising properties could also be involved in the future.[12] In analogy to the Sanofi synthesis, the multicomponent reactions described here only yielded clopidogrel **4** as a racemic mixture and a further resolution-step will be necessary to yield the drug (*S*)-clopidogrel (**1**). For example, a possible resolution[11] consists of mixing the racemic clopidogrel with levorotatory camphor-10-sulfonic acid in acetone. The resulting salt can be recrystallized from acetone to generate (*S*)-clopidogrel (**1**). Further scale-up experiments and studies on the cost of building blocks could determine whether the reaction is suitable for industrial application and lead to a price reduction of this marketed product.

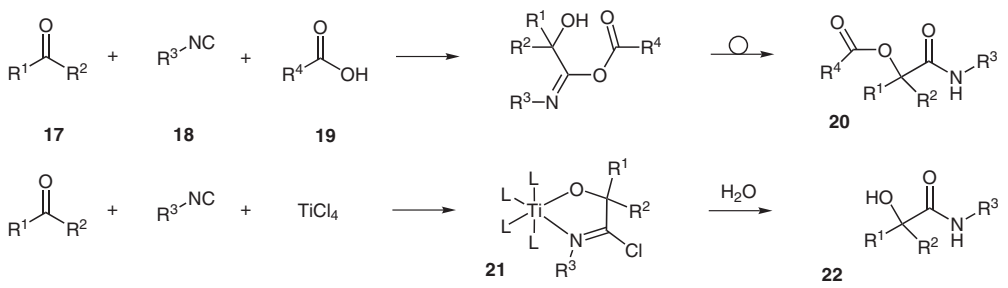
As a second illustration of the potential use of MCRs in the field of generic drug production, we present a short, efficient, two-step synthesis of the non-steroidal antiandrogen bicalutamide (**16**; Casodex®), which is the leading antiandrogen used for the treatment of prostate cancer.[13] The key step is a Passerini reaction (P-3CR) assisted by titanium tetrachloride (Scheme 4). The Passerini reaction is a classical MCR discovered in the 1920s.[14] The reaction between a carbonyl compound **17**, an isocyanide **18** and a carboxylic acid **19**, leads to the formation of an α-hydroxy amide ester **20** (Scheme 5). In a variation of the original P-3CR method, protic mineral acids and Lewis acids such as titanium tetrachloride are used as promoters.[15]

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.[16] 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,[17] 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[18] and a two-step synthesis via 1,2-addition of a methyl sulfone to a keto amide.[19] 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)phenylisocyanide (**15**) can be prepared from the corresponding aniline following known procedures[20] and is commercially available.



Scheme 4 Synthesis of (*R*,*S*)-bicalutamide (**16**) via a titanium tetrachloride assisted Passerini reaction



Scheme 5 Classical Passerini reaction versus titanium tetrachloride assisted Passerini reaction (L = Cl or donor group of substrate)

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 bicalutamide 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*)-Clopidogrel 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*)-bicalutamide via a titanium tetrachloride assisted Passerini reaction has been developed.

^{1}H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with a Bruker AV 250 spectrometer. Chemical shifts are expressed in ppm (δ) with respect to TMS as an internal standard. Electrospray ionization mass spectra (ESI) were obtained using a Varian 1200 L Quadrupole MS/MS. Purity was determined with a Varian LC Prostar 325 system [Varian Polaris RP C18 column; 3 mm × 150 mm; 5 μm ODSA; 215 nm and 254 nm; 1 mL/min, 3 min gradient from 90% H_2O to 10% H_2O (0.5% HCOOH) vs. MeCN (0.5% HCOOH)].

All starting materials used are commercially available. Isocyanides **7** and **15** are available from Priaxon AG. Compound **14** is now commercially available from Otava.

2-(2-Chlorophenyl)-*N*-cyclohex-2-enyl-2-(6,7-dihydro-4*H*-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 Et_3N (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 CH_2Cl_2 (20 mL), washed with brine (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over $MgSO_4$, evaporated to dryness and purified on a silica gel column (EtOAc–hexane, 1:3) to give **8**.

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

^{1}H NMR ($CDCl_3$, 250 MHz): δ = 8.36 (s, 1 H), 7.44–7.40 (m, 2 H), 7.28–7.24 (m, 2 H), 7.08 (d, ^3J = 5.2 Hz, 1 H), 6.66 (d, ^3J = 5.0 Hz, 1 H), 6.16 (t, ^3J = 11.4 Hz, 1 H), 4.89 (s, 1 H), 3.62 (dd, ^3J = 7.4 Hz, ^2J = 14.4 Hz, 2 H), 2.9 (s, 4 H), 2.16–2.10 (m, 4 H), 1.74–1.55 (m, 4 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 168.6, 135.6, 133.6, 133.2, 139.9, 130.4, 130.1, 129.4, 127.0, 125.3, 123.1, 113.0, 69.7, 50.7, 49.2, 28.0, 26.0, 23.9, 22.5, 21.9.

MS (+ESI): *m*/*z* = 387 $[M + H]^+$.

IR: 3303, 2925, 2835, 1686, 1509, 1472, 1437, 1219, 1038, 1017, 753, 702 cm^{-1}.

(2-Chlorophenyl)-(6,7-dihydro-4*H*-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–HCl_{aq} [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 CH_2Cl_2 (20 mL), washed with brine (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The aqueous layer was made basic with sat. $NaHCO_3$ (~0.5 mL) until pH 8, and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layer was dried over $MgSO_4$, evaporated to dryness, and the product was crystallized (Et_2O–hexane) to give **3**.

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

^{1}H NMR ($CDCl_3$, 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, ^3J = 5.2 Hz, 1 H), 6.66 (d, ^3J = 5.0 Hz, 1 H), 4.94 (s, 1 H), 3.65 (dd, ^3J = 7.9 Hz, ^2J = 14.4 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 173.0, 135.4, 132.9, 130.4, 130.1, 129.6, 127.1, 125.2, 123.2, 69.0, 50.8, 49.1, 25.7.

MS (+ESI): *m*/*z* = 308 $[M + H]^+$.

IR: 3468, 2923, 2358, 1655, 1578, 1418, 1255, 1090, 1034, 954, 751, 700 cm^{-1}.

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

To a solution of glyoxylic acid monohydrate (**9**; 30 mg, 0.33 mmol) in DMF (1 mL) was added 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**5**; 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 H_2O (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL) and the combined organic layer was dried over $MgSO_4$, 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*)-Clopidogrel (4) from 3

To a solution of **3** (20.0 mg, 0.065 mmol) in MeOH (2 mL) was added concd H_2SO_4 (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 CH_2Cl_2 (10 mL). The organic layer was washed with sat. $NaHCO_3$ (5 mL), dried over $MgSO_4$ and evaporated to yield **4**.

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

^{1}H NMR ($CDCl_3$, 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, ^3J = 5.0 Hz, 1 H), 6.66 (d, ^3J = 5.2 Hz, 1 H), 4.92 (s, 1 H), 3.72 (s, 3 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-4*H*-thieno[3,2-*c*]pyridin-5-yl)acetylamino}-1,1-dimethylethyl 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 Et_3N (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 carbonate (**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 CH_2Cl_2 (20 mL) and washed with brine (10 mL). The obtained aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layers were dried over $MgSO_4$, 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.

^{1}H NMR ($CDCl_3$, 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, 3 H), 1.45 (s, 6 H).

^{13}C NMR ($CDCl_3$, 63 MHz): δ = 170.9, 154.0, 135.3, 133.5, 133.4, 133.1, 130.3, 130.0, 129.3, 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}.

(*R*,*S*)-Clopidogrel (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 CH_2Cl_2 (20 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layer was dried over $MgSO_4$, evaporated to dryness and purified on a silica gel column (EtOAc–hexane, 1:1.5) to give **4** as a colorless oil (41 mg, 42%). Analytical data were in accordance with those observed for the same product synthesized from **3**.

1-(4-Fluorophenylsulfonyl)propan-2-one (14)

MCPBA (8.96 g, 52 mmol) was added to a solution of (4-fluorophenylthio)acetone (**13**; 3.18 g, 17.3 mmol) in CH_2Cl_2 (75 mL). The solution was stirred at r.t., during which time a white precipitate formed. After 2 h, TLC (silica gel, EtOAc–$CHCl_3$, 1:1) indicated complete conversion of the starting materials. The precipitate was removed by filtration and washed with CH_2Cl_2 (10 mL). The clear solution was evaporated to dryness and the residue was purified by recrystallization (EtOAc–hexane) to give **14**.

Yield: 3.43 g (92%); white solid.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.92 (dd, $^3J_{H–H}$ = 8.5 Hz, $^4J_{H–F}$ = 5.0 Hz, 2 H), 7.26 (app t, $^3J_{H–H}$ = $^3J_{H–F}$ = 8.5 Hz, 2 H), 4.16 (s, 2 H, CH_2), 2.42 (s, 3 H, CH_3).

(*R*,*S*)-Bicalutamide (16)

4-Cyano-3-(trifluoromethyl)phenylisocyanide (**15**; 0.67 g, 3.5 mmol) was dissolved in anhydrous CH_2Cl_2 (20 mL) and cooled in an ice–water bath. $TiCl_4$ (1 M in CH_2Cl_2, 3.9 mL, 1.2 equiv) was added, (a precipitate was formed) and the resulting suspension was stirred for 1 h. 1-(4-Fluorophenylsulfonyl)propan-2-one (**14**; 0.76 g, 3.5 mmol) was added and the mixture was stirred until TLC (silica gel, EtOAc–hexane, 1:1) indicated complete consumption of the starting materials (~3 h). H_2O (20 mL) was added and the mixture was stirred for another 20 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 10 mL). The pooled organic phases were washed with sat. $NaHCO_3$ (15 mL), H_2O (15 mL) and brine (15 mL). After drying over $MgSO_4$, the solvent was removed in vacuo and the residue was crystallized (EtOAc–hexane) to afford **16** with >99% purity.

Yield: 0.99 g (66%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.99–7.87 (m, 3 H), 7.41–7.22 (m, 4 H), 4.3 (br s, 1 H, OH), 3.93 (d, ^2J = 14.5 Hz, 1 H, CH_2), 3.62 (d, ^2J = 14.5 Hz, 1 H, CH_2), 1.67 (s, 3 H, CH_3). Data are in accordance with those previously published.[18]

References

(1) (a) Dömling, A.; Ugi, I. *Angew. Chem. Int. Ed.* **2000**, *39*, 3168. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.
(2) Hulme, C. In *Multicomponent Reactions*; Zhu, J.; Bienayme, H., Eds.; Wiley-VCH: Weinheim, **2005**.
(3) (a) Rossen, K.; Pye, P. J.; DiMichele, L. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 6823. (b) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Wells, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673.
(4) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.
(5) (a) Gurbel, P. A.; O'Connor, C. M.; Cummings, C. C.; Serebruany, V. L. *Pharm. Res.* **1999**, *40*, 107. (b) Jacobson, A. K. *Best Pract. Res. Clin. Haematol.* **2004**, *17*, 55.
(6) (a) Ugi, I.; Meyer, R.; Fetzer, U.; Steinbrückner, C. *Angew. Chem.* **1959**, *71*, 386. (b) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 8. (c) Dömling, A.; Ugi, I. *Angew. Chem.* **2000**, *112*, 3300.
(7) Keating, T. A.; Armstromg, W. *J. Am. Chem. Soc.* **1996**, *118*, 2574.
(8) Petasis, N. A.; Akritopoulou, I. *Tetrahedron Lett.* **1993**, *34*, 583.
(9) Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445.
(10) Lindhorst, T.; Bock, H.; Ugi, I. *Tetrahedron* **1999**, *55*, 7411.
(11) (a) Eliel, E. L.; Fisk, M. T.; Prosser, T. *Org. Synth. Coll. Vol. IV*; John Wiley & Sons: London, **1963**, 169. (b) Aubert, D.; Ferrand, C.; Maffrand, J.-P. French Patent FR2530247, **1984**. (c) Badorc, A.; Frehel, D. US Patent 4847265, **1989**. (d) Tucker, H. US Patent 4636505, **1987**. (e) Soeroes, B.; Tuba, Z.; Galik, G.; Bor, A.; Demeter, A.; Trischler, F.; Horvath, J.; Brlik, J. US Patent 7199257, **2007**.
(12) (a) Pirrung, M. C.; Ghorai, S. *J. Am. Chem. Soc.* **2006**, *128*, 11772. (b) Kreye, O.; Westermann, B.; Wessjohann, L. A. *Synlett* **2007**, 3188. (c) Gilley, C. B.; Buller, M. J.; Kobayashi, Y. *Org. Lett.* **2007**, *9*, 3631.
(13) (a) Masiello, D.; Cheng, S.; Bubley, G. J.; Lu, M. L.; Balk, S. P. *J. Biol. Chem.* **2002**, *29*, 26321. (b) Hodgson, M. C.; Astapova, I.; Hollenberg, A. N.; Balk, S. P. *Cancer Res.* **2007**, *67*, 8388.
(14) (a) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) Passerini, M. *Gazz. Chim. Ital.* **1921**, *51*, 181.
(15) (a) Schiess, M.; Seebach, D. *Helv. Chim. Acta* **1983**, *66*, 1618. (b) Seebach, D.; Adam, G.; Gees, T.; Schiess, M.; Weigand, W. *Chem. Ber.* **1988**, *121*, 507. (c) Seebach, D.; Beck, A. K.; Schiess, M.; Widler, L.; Wonnacott, A. *Pure Appl. Chem.* **1983**, *55*, 1807.
(16) Carofiglio, T.; Cozzi, P. G.; Floriani, C. *Organometallics* **1993**, *12*, 2726.
(17) Semple, J. E.; Owens, T. D.; Nguyen, K.; Levy, O. E. *Org. Lett.* **2000**, *2*, 2769.
(18) James, K. D.; Ekwuribe, N. N. *Tetrahedron* **2002**, *58*, 5905.
(19) James, K. D.; Ekwuribe, N. N. *Synthesis* **2002**, 850.
(20) Obrecht, R.; Herrmann, R.; Ugi, I. *Synthesis* **1985**, 400.