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# A novel route to 2,4-dianilino-substituted pyrimidines ☆

Ruben Leenders [a,*], Jan Heeres [b], Jérôme Guillemont [c], Paul Lewi [b]

[a] Mercachem BV, Kerkenbos 10-13, 6546 BB Nijmegen, The Netherlands
[b] Janssen Research Foundation, Center for Molecular Design, Antwerpsesteenweg 37, B-2350 Vosselaar, Belgium
[c] Johnson and Johnson Pharmaceutical Research and Development, Medicinal Chemistry Department, Campus de Maigremont BP315, F-27106 Val de Reuil Cedex, France

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ABSTRACT

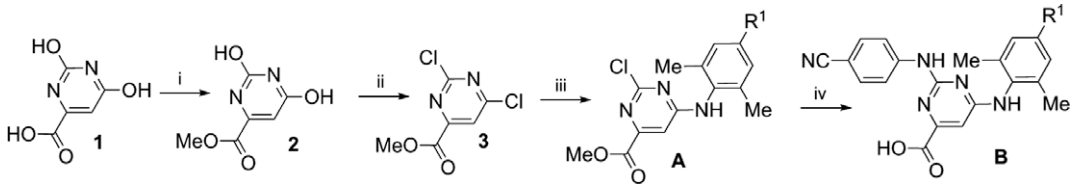
A method is described to couple sterically-hindered electron-poor anilines to the 4-position of the pyrimidine core using a pyrimidine-2,4-bis(trifluoromethanesulfonate).



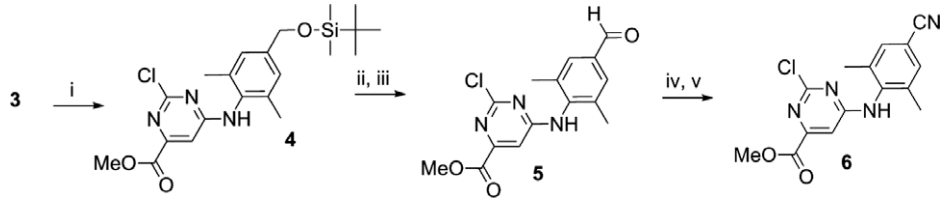
In our continuing search toward HIV-inhibiting pyrimidines,[1,2] we have prepared a series of 2,4-anilino disubstituted pyrimidines derived from orotic acid (**1**, Scheme 1). These compounds act as non-nucleoside reverse transcriptase inhibitors (NNRTIs). In the present Letter we outline this synthesis.

Using route A (Scheme 1), in the first step, 2,6-dichloropyrimidine-4-carboxylic acid methyl ester (**3**)[3] was functionalized selectively at the 4-position with an aniline yielding structure **A**. Next, the 2-position was substituted with 4-cyanoaniline under acidic conditions to furnish **B**.

This route, however, did not work where $R^1$ was an electron-withdrawing group, for example, 2,6-dimethyl-4-cyanoaniline did not react with dichloride **3** under any of the conditions tested.[4] In addition, we prepared amides of 2,6-dimethyl-4-cyanoaniline (acetate, trifluoroacetate, and benzoate) to enable abstraction of the remaining –NH and making the aniline more nucleophilic,




**Scheme 1.** Route A. Reagents and conditions: (i) MeOH, $H_2SO_4$, $(MeO)_2CO$, reflux, 48 h (96%); (ii) $POCl_3$, reflux, 16 h (80%); (iii) $R^1$ = Me: 2,4,6-trimethylaniline, DIPEA, THF, rt, 48 h (81%); and (iv) $R^1$ = Me: 4-cyanoaniline, BuOH, HCl, $H_2O$, 100 °C, 16 h (98%).




**Scheme 2.** Route B. Reagents and conditions: (i) 4-[(*tert*-butyldimethylsilyloxy)methyl]-2,6-dimethylaniline, DIPEA, THF, reflux, 48 h (26%); (ii) MeOH, PPTS, reflux, 30 min; (iii) acetone, $MnO_2$, rt, 1 h (41% over two steps); (iv) hydroxylamine–HCl, $Et_3N$, MeCN, rt, 16 h; and (v) Burgess reagent, THF, reflux, 4 h (30% over two steps).

☆ See Ref. 1.

* Corresponding author. Tel.: +31 (0) 24 372 3321; fax: +31 (0) 24 372 3305.
*E-mail addresses:* ruben.leenders@mercachem.com, rggleenders@gmail.com (R. Leenders).

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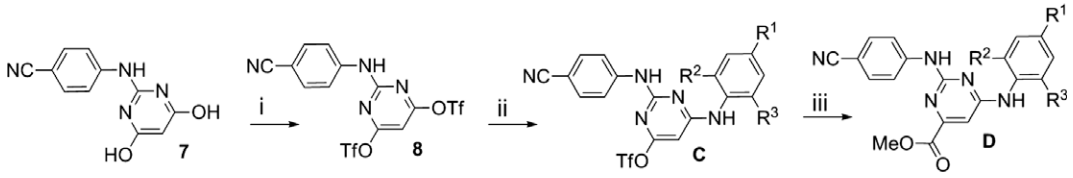
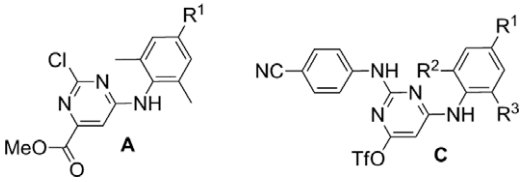


**Scheme 3.** Route C. Reagents and conditions: (i)[5] $Tf_2O$, $Et_3N$, $CH_2Cl_2$, 0 °C to rt, 16 h (50%); (ii) $R^1R^2R^3$-substituted aniline, THF, reflux, 16 h (10–40%); and (iii)[6] carbon monoxide, MeOH, $Pd(OAc)_2$dppf, $Et_3N$, DMF, 80 °C, 4–16 h (60–80%).

**Table 1**
List of products of type **A** and **C**



| Entry | Route | Product | $R^1$ | $R^2$ | $R^3$ | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | A | **A** | Me | Me | Me | 81[a] |
| 2 | A | **A** | $CH_2CN$ | Me | Me | 26[a] |
| 3 | A | **A** | $CH_2CH_2CN$ | Me | Me | 20[a] |
| 4 | B | **A** | CN | Me | Me | 26[b] |
| 5 | B | **A** | CH=CHCN | Me | Me | 26[b,c] |
| 6 | C | **C** | CH=CHCN | Me | OMe | 20[d] |
| 7 | C | **C** | CH=CHCN | Cl | OMe | 11[d] |
| 8 | C | **C** | CH=CHCN | Me | H | 28[d] |
| 9 | C | **C** | CH=C(Me)CN | Me | Me | 36[d] |

[a] Yield of **3** to **A**, Scheme 1.
[b] Yield of **3** to **4**, Scheme 2.
[c] From **5** (Scheme 2) this product is prepared via a Wittig reaction with diethyl cyanomethylphosphonate (76% yield).
[d] Yield of **8** to **C**, Scheme 3.

however, coupling with **3** did not proceed. Alternatively, following route B (Scheme 2), we were able to prepare the desired coupled product **6**. In this route, protected benzyl alcohol intermediate **4** was transformed into the corresponding aldehyde and then to the oxime which was dehydrated to give the nitrile **6**.

As this route was quite laborious and the yields were low, we developed an alternative route. In route C (Scheme 3), 4,6-dihydroxypyrimidine **7**[2a] was converted into ditriflate **8**. One of the triflate groups was substituted with an aniline moiety to give intermediate **C** and the remaining triflate group was transformed into a methyl ester by palladium-mediated carbonylation in the presence of methanol to afford **D**.

This synthesis shows that the highly reactive ditriflate **8**[5] is a valuable synthon in pyrimidine synthesis. One triflate group can even be replaced with a bis-*ortho*-substituted electron-poor aniline such as 2,6-dimethyl-4-cyanoaniline, whereas the corresponding chloride did not react at all. See Table 1 for a list of the compounds prepared. Carbonylation of the remaining triflate group was performed in good yields (60–80%).[6] This is a rarely described process in the literature.[7]

## References and notes


1. Some of the compounds described in this Letter were claimed in Kukla, M. J.; Ludovici, D. W.; Kavash, R. W.; De Corte, B. L. D.; Heeres, J.; Janssen, P. A. J.; Koymans, L. M. H.; De Jonge, M. R.; Van Aken, K. J. A.; Krief, A.; Leenders, R. G. G. U.S. 7276510, 2007; *Chem. Abstr.* **2001**, *135*, 371765. The synthesis of the compounds from route C (Scheme 3) were not described in this patent.
2. (a) Ludovici, D. W.; De Corte, B. L.; Kukla, M. J.; Ye, H.; Ho, C. Y.; Lichtenstein, M. A.; Kavash, R. W.; Andries, K.; de Béthune, M.-P.; Azijn, H.; Pauwels, R.; Lewi, P. J.; Heeres, J.; Koymans, L. M. H.; De Jonge, M. R.; Van Aken, K. J. A.; Daeyaert, F. F. D.; Das, K.; Arnold, E.; Janssen, P. A. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2235; (b) De Corte, B.; De Jonge, M. R.; Heeres, J.; Ho, C. Y.; Janssen, P. A. J.; Kavash, R. W.; Koymans, L. M. H.; Kukla, M. J.; Ludovici, D. W.; Van Aken, K. J. A. WO 2000/27825; *Chem. Abstr.* **2000**, *132*, 347578.; (c) Kukla, M. J.; Ludovici, D. W.; Kavash, R. W.; De Corte, B. L. D.; Heeres, J.; Janssen, P. A. J.; Koymans, L. M. H.; De Jonge, M. R.; Van Aken, K. J. A.; Krief, A. U.S. 7034019; *Chem. Abstr.* **2001**, *135*, 371756.; (d) Schils, D. P. R.; Willems, J. J. M.; Medaer, B. P. A. M.; Pasquier, E. T. J.; Janssen, P. A. J.; Heeres, J.; Leenders, R. G. G. WO 2004/016581; *Chem. Abstr.* **2004**, *140*, 199342.; (e) Guillemont, J. E. G.; Paugam, M.; Delest, B. F. M. Patent WO 2007/113254; *Chem. Abstr.* **2007**, *147*, 427364.; (f) Guillemont, J.; Pasquier, E.; Palandjian, P.; Vernier, D.; Gaurrand, S.; Lewi, P. J.; Heeres, J.; De Jonge, M. R.; Koymans, L. M. H.; Daeyaert, F. F. D.; Vinkers, M. H.; Arnold, E.; Das, K.; Pauwels, R.; Andries, K.; De Béthune, M.-P.; Bettens, E.; Hertogs, K.; Wigerinck, P.; Timmerman, P.; Janssen, P. A. J. *J. Med. Chem.* **2005**, *48*, 2072; (g) Mordant, C.; Schmitt, B.; Pasquier, E.; Demestre, C.; Queguiner, L.; Masungi, C.; Peeters, A.; Smeulders, L.; Bettens, E.; Hertogs, K.; Heeres, J.; Lewi, P.; Guillemont, J. *Eur. J. Med. Chem.* **2007**, *42*, 567.
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4. We tested different organic and inorganic bases in THF, DME, dioxane, DMF, or DMAc, microwave irradiation, and Buchwald–Hartwig coupling conditions [$Pd(OAc)_2$, BINAP, $Cs_2CO_3$, toluene, 80 °C]. However, no trace of the desired product was found using any of these conditions.
5. *Synthesis of* **8**: 3.64 g of **7** was stirred in 150 mL of dry $CH_2Cl_2$ and 4.45 mL of $Et_3N$ (2 equiv) for 2 h and then cooled to 0 °C. Next, 9.0 g of $Tf_2O$ (2 equiv) in 50 mL of $CH_2Cl_2$ was added slowly to the substrate and the resulting mixture was stirred overnight while the temperature was allowed to reach rt. The reaction was washed with $H_2O$ (1 × 200 mL) (when satd aq $NaHCO_3$ was used instead of $H_2O$, the product decomposed), the organic layer was dried and the solvent was evaporated leaving 3.9 g (50%) of a creamy solid behind. $R_f$ = 0.45 ($SiO_2$, heptane–EtOAc, 3:1); $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 6.38 (s, 1H), 7.70 (br s, 4H). The product was used as such.
6. *Typical procedure*: 1.73 mmol of triflate **C**, 6 mol % of dppf and 3 mol % of $Pd(OAc)_2$ were dissolved in 25 mL of dry DMF and the mixture was degassed by bubbling a flow of nitrogen through the solution. Next, 50 equiv of MeOH and 3 equiv of $Et_3N$ were added and CO was bubbled through the solution until saturation. The reaction vessel was closed and heated at 80 °C. When the reaction was complete (4–12 h) it was cooled to rt, flushed with nitrogen and partitioned between $H_2O$ and EtOAc. The organic extract was dried, evaporated and the residue was purified by column chromatography (EtOAc–heptane) to give the product methyl esters **D** in 60–80% yield.
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