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2-Fluoropyrimidine as an efficient reagent in solid-phase synthesis of *N*-aryl- and *N*-alkyl-*N*-pyrimidin-2-ylamines

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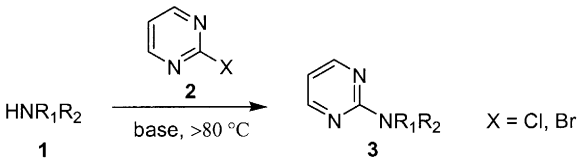
Abstract

Mild and efficient reaction conditions were developed for the solid-phase synthesis of *N*-aryl- and *N*-alkyl-*N*-pyrimidin-2-ylamines. 2-Fluoropyrimidine in the presence of DIEA showed suitable properties for reactions with resin-bound alkylamines at room temperature. Since anilines proved to be inert under these conditions, an alternative approach was developed using $BF_3 \cdot Et_2O$ as a potent catalyst for the reaction of anilines with 2-fluoropyrimidine. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: catalysis; combinatorial chemistry; pyrimidines; solid-phase synthesis.

Within the last few years solid-phase supported combinatorial synthesis has become established in medicinal chemistry.[1] 2-Aminopyrimidine (**3**) is an interesting structural element that is found in compounds with potential biological functions as diverse as antipsychotic,[2a] cardioprotective,[2b] and antimalarial[2c] activities. Several examples of 2-aminopyrimidine-containing compounds have resulted in marketed drug substances.[3] We intended to employ this heterocycle as a guanidine mimetic in our aza-Arg-Gly-Asp (RGD) libraries[4] in order to improve their pharmacological properties based on the observation that this replacement can result in compounds with enhanced Caco-2 cell permeability.[5] A common approach for this class of compounds is the conversion of amines or anilines (**1**) via aromatic nucleophilic substitution with 2-chloro- or 2-bromopyrimidine (**2,** X=Cl, Br) (Scheme 1). However, the required harsh reaction conditions (>80°C) restrict a broad application of this method in solid-phase



Scheme 1. Conventional solution-phase synthesis of *N*-substituted *N*-pyrimidin-2-ylamines via 2-halogenopyrimidines

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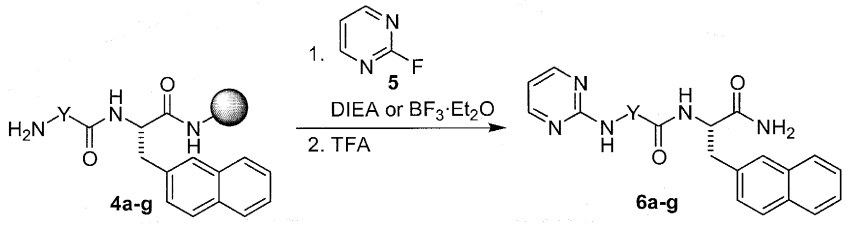
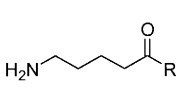
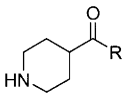
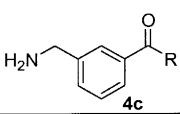
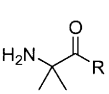


Scheme 2. Solid-phase supported synthesis of *N*-aryl- and *N*-alkyl-*N*-pyrimidin-2-ylamine **6a**–**g**. For explanation of Y see Tables 1 and 2

Table 1
Solid-phase supported conversion of amines **4a**–**d** into the corresponding *N*-alkyl-*N*-pyrimidin-2-ylamine **6a**–**d** using 2-fluoropyrimidine (**5**) and DIEA as the reagents

resin-bound amines[a]		 **4a**	 **4b**	 **4c**	 **4d**
cond.[7]	**time**	**reaction progress**[b] **(%)**			
5 (3 eq., 0.1 M),	7 h	89	98	60	2
DIEA (3 eq.,	1 d	98	99	88	4
0.1 M), DMF,	2 d	98	99.5	93	4
25 °C	4 d	99	>99.5	95	9
5 (15 eq., 0.5 M),	7 h	99	99.5	95	3
DIEA (15 eq.,	1 d	99	>99.5	96	6
0.5 M), DMF,	2 d	99	>99.5	97	10
25 °C	4 d	99.5	>99.5	97	26
product		**6a**	**6b**	**6c**	**6d**
ESI-MS		392 [M+H$^+$]	304 [M+H$^+$]	464 [M+K$^+$]	400 [M+Na$^+$]
purity[c] **(%)**		96	>99.5	95	92

[a] R = 2-Nal-Rink amide MBHA resin
[b] The reaction progress was determined by the relative integral intensities of the product and the starting material obtained from the reversed-phase HPLC-chromatogram at 220 nm.
[c] Reversed-phase HPLC at 220 nm taken from the last entry; the remaining starting material was disregarded.

synthesis. Here, we describe mild and efficient methods for the conversion of resin-bound aliphatic amines **4a**–**d** and anilines **4e**–**g** into the corresponding *N*-substituted *N*-pyrimidin-2-ylamines **6a**–**g**.

A standard Fmoc-peptide coupling protocol was used to synthesise the amino acid 2-naphthylalanines (Xaa-2-Nal) **4a**–**g** on Rink amide MBHA resin as immobilised model amines and anilines (Scheme 2). The predominant UV-chromophor 2-Nal was incorporated to facilitate reliable quantification of the reaction progress by HPLC chromatogram detected at 220 nm. Since 2-fluoropyrimidine (**5**) exhibited in a kinetic study an approximately 100-fold higher reaction rate in the conversion of piperidine than the chloro- or bromo-counterparts,[6] it became our reagent of choice. Remarkably, to our knowledge, the high reactive 2-fluoropyrimidine (**5**) has never been used for the preparation of 2-aminopyrimidines except in kinetic studies with piperidine.[6]

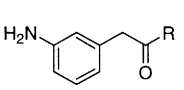
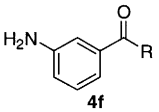
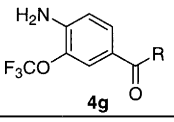
Table 1 shows that the reaction of the aliphatic amines **4a**–**b** were almost complete within 1 day, using a 0.1 M solution of **5** and DIEA in DMF.[7] The benzylamine **4c** turned out to be less reactive, but sufficient enhancement of the reaction rate was achieved by increasing the concentration of **5** and DIEA.

The sterically hindered amine **4d**, however, showed significantly slower reaction rates. As a result, we excluded related compounds in the design of our libraries.

The conversion of anilines with the procedure described above completely failed: even treatment of the resin-bound aniline **4f** with an excess of 2-fluoropyrimidine (**5**) and DIEA at 50°C afforded no detectable amounts of **6f**. We assumed that protonation of an N-atom of 2-fluoropyrimidine (**5**) with a suitable acid may result in a more electrophilic species, whereas the anilines as poor bases are largely unprotonated, and therefore should remain nucleophilic. Indeed, trifluoroacetic acid, and also $BF_3 \cdot Et_2O$, proved to be effective catalysts for the reaction of anilines with 2-fluoropyrimidine (**5**). $BF_3 \cdot Et_2O$ became our preferred reagent, since it is compatible with *tert*-butylester used in our libraries as a permanent protecting group.

The results of Lewis acid catalysed conversion of the anilines **4e–g** into the corresponding 2-aminopyrimidines **6e–g** are shown in Table 2.[8] At room temperature, anilines **4e–f** must be treated for 7 days with a 1.0 M solution of **5** to enforce complete reaction, whereas an acceptable increase of the temperature to 50°C shortened the reaction time to 2 days. The electron deficient aniline **4g** also underwent the reaction, but with a rather unsatisfactory reaction rate.

Table 2
Solid-phase supported conversion of anilines **4e–f** into the corresponding *N*-aryl-*N*-pyrimidin-2-ylamine **6e–f** using 2-fluoropyrimidine (**5**) and $BF_3 \cdot Et_2O$ as the reagents

resin-bound anilines[a]		 **4e**	 **4f**	 **4g**
cond.[8]	**time**	**reaction progress**[b] **(%)**		
	7 h	26	40	0
5 (30 eq., 1.0 M),	1 d	58	76	2
5% $BF_3 \cdot Et_2O$	2 d	80	93	5
in DMF, 25 °C	4 d	95	99	10
	7 d	99.5	>99.5	18
	7 h	82	95	5
5 (30 eq., 1.0 M),	1 d	98	>99.5	15
5% $BF_3 \cdot Et_2O$	2 d	>99.5	>99.5	23
in DMF, 50 °C	4 d	>99.5	>99.5	34
	7 d	>99.5	>99.5	42
product		**6e**	**6f**	**6g**
ESI-MS		426 [M+H$^+$]	412 [M+H$^+$]	496 [M+H$^+$]
purity[c] **(%)**		99	99	90

[a] See footnote *a* of Table 1; [b] See footnote *b* of Table 1; [c] See footnote *a* of Table 1.

As expected, the aliphatic amines **4a–d** could not be converted into the corresponding 2-aminopyrimidines **6a–d** with the Lewis acid method. Therefore, we first treat libraries containing mixtures of aliphatic amines and anilines with **5** and DIEA followed by thorough washing, before applying the $BF_3 \cdot Et_2O$-catalysed approach. By this reaction protocol we achieved high yields and high purity of all components.

In conclusion we have developed mild and efficient reaction conditions for the conversion of both aliphatic amines and anilines into the corresponding *N*-pyrimidin-2-ylamines on a solid support using 2-fluoropyrimidine as the reagent. We have demonstrated the feasibility of these approaches by the

conversion of different resin-bound aliphatic amines and anilines. The required low temperatures and the moderate pH values provide a high degree of compatibility with diverse molecules and therefore meet the requirements of combinatorial chemistry.

Acknowledgements

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3. For example: Buspirone (tranquilizer), CAS Registration Number (RN): 36505-84-7; Piribedil (vasodilator), RN: 3605-01-4; Tandospirone (anxiolytic, antidepressant), RN: 87760-53-0.
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7. Experimental procedure: A polypropylene 0.5 mL reaction vessel was loaded with amine resin **4a**–**d** (30 mg, 0.20 mmol/g, 6.0 μmol). The resin was suspended in a solution of 2-fluoropyrimidine (**5**) (8.9 mg, 90 μmol, 15 equiv.) and DIEA (15 μL, 12 mg, 90 μmol, 15 equiv.) in anhydrous DMF (180 μL) and the vessel was rotated at 30 rpm. In order to monitor the reaction progress, a small sample of the reaction suspension (15 μL) was transferred with a microliter pipette into a 2 mL syringe with a fritted disc. The resin was washed with DMF (4×1 mL) and CH_2Cl_2 (3×1 mL) and then cleaved with 95:5 TFA:H_2O (1 mL) for 60 min. The supernatant was concentrated in vacuo and the residue was resolved in CH_3CN (1 mL). This solution was directly used for HPLC and ESI-MS analysis.
8. According to the procedure described in Ref. 7, using 2-fluoropyrimidine (**5**) and $BF_3 \cdot Et_2O$ as the reagents.