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Microwave assisted solid-phase synthesis of trisubstituted 2-(2,6-purin-9-yl)acetamides

Richard E. Austin,[a] Christian Waldraff[b] and Fahad Al-Obeidi[a,*]

[a]*ACTC, Aventis Combinatorial Technologies Center, 1580 E. Hanley Blvd., Tucson, AZ 85737, USA*
[b]*Hit Discovery Group, Bayer CropScience, D-65926 Frankfurt of Main, Germany*

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Abstract—In the course of developing a method for the parallel synthesis of purin-9-yl-acetamides, it was found that microwave irradiation was beneficial in accelerating the nucleophilic displacement of halogens by amines at the C-2 position of the purine nucleus.

1. Introduction

Because the purine scaffold is present in many natural products and analogs capable of mediating biochemical processes, several methods for the high-throughput synthesis of purine derivatives have been developed.[1–8] Many of the reported protocols share in common the nucleophilic displacement of a halogen at the C-2 position of the purine, a reaction typically requiring high temperature and long exposure. While developing a method for the parallel synthesis of purin-9-yl-acetic acid derivatives this transformation was most troublesome.

Employment of microwave irradiation to not only heat but accelerate chemical reactions is now common practice in modern chemistry.[9] Despite uncertainty in identifying the source of increased reaction rates,[10] this mode of heating has been applied to resin bound molecules with positive results relative to conventional heating techniques.[11–16] In this work, microwave-induced heating proved to be the key in enabling the synthesis of a 20,000 member chemical library of structurally diverse purin-9-yl-acetamides.

2. Results and discussion

As a scaffold, a 2,6-dihalopurine bearing an acetic acid appendage at N-9 (Scheme 1) was chosen. This selection was made to offer a measure of novelty relative to other high-throughput synthetic work in the area[1–6] and to provide a common, functional handle for attachment of the scaffold to solid support. The investigation began with commercially available 2,6-dichloropurine that was reacted with *t*-butyl bromoacetic acid, according to a modified, literature procedure,[17] to provide a mixture of N-9 and N-7 regioisomers. Subsequent treatment with TFA and crystallization afforded the N-9 isomer **2**. The scaffold was coupled (DIC/HOAt) to a polystyrene resin bearing a secondary amine attached via a dialkoxybenzyl linker (**1**) to deliver **5** (X = Cl).

Displacement of the C-6 chloro substituent with primary and secondary aliphatic and benzylic amines was straightforward in NMP at 60 °C (conventional heating, 1–2 h) to give **6**. Addition of anilines was achieved, employing the aniline as the reaction solvent (120 °C, 3 h).

The displacement of the C-2 chloro substituent by amines proved to be difficult and became the focus of the investigation. A complicating factor was the intention to develop a method for the parallel synthesis of purine derivatives and the corresponding need, under conventional protocols, for an apparatus to accommodate multiple reaction vessels, high temperatures, and long reaction times. In sealed glass vials employing strongly nucleophilic amines, the displacement of the C-2 chloro substituent was accomplished at elevated temperatures (120–150 °C) over a period of 24 h with high levels of conversion. Reactions involving amines of reduced nucleophilicity (e.g., those bearing

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* Corresponding author. Tel.: +1 520 544 5879; fax: +1 520 575 8283; e-mail: fahad.al.obeidie@aventis.com

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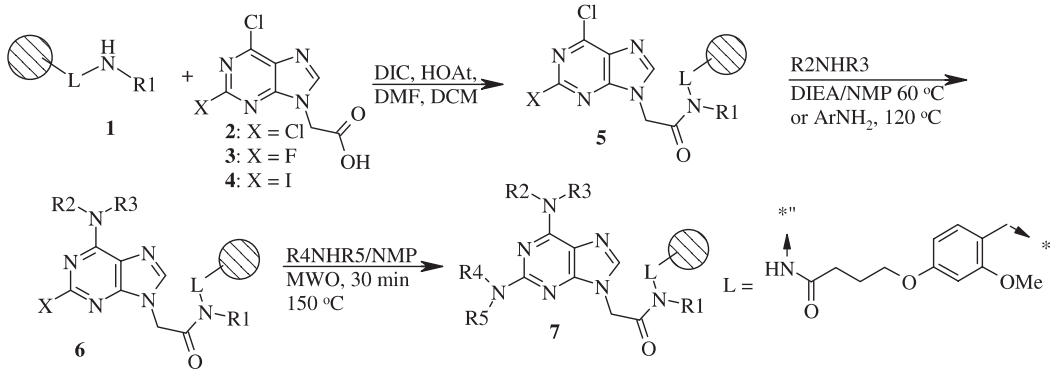


Scheme 1.

β-heteroatoms) required longer reaction times and often would not go to completion. With the harsh conditions came the observation of by-products attributed to thermal decomposition of resin and reactants. Undeterred, the same chemistry was attempted in deep well microtiter plates. Owing to the high temperatures, a variety of glass, aluminum, and Teflon plates were tested. The results observed mirrored those obtained in glass vials. However it was difficult to adequately seal the plates. In the case of volatile amines, reactions would not go to completion owing to the amine being driven off at elevated temperatures. In some cases, volatile amines would migrate to neighboring wells leading to products of apparent cross-contamination.

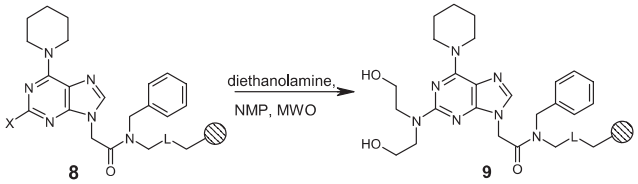
Reports of enhanced reaction rates when using microwave irradiation for heating reaction mixtures prompted investigation of this alternative beginning with an ordinary, household microwave oven. With the correct setting, single reactions could be driven to completion in 30 min or less compared to 24 h with conventional heating techniques. Difficulty was encountered when scaling up the amounts of starting materials or when the number of reaction vessels used at a single time was increased. When a method optimized on a single vessel with a small amount of resin (ca. 10 mg) was transferred to a larger run, evaporation of the solvent, damaging of the resin, and unpredictable levels of conversion typically resulted. To alleviate this problem, a microwave oven featuring thermo-optic feedback of temperature to the magnetron was purchased[18] to control the level of irradiation. Methods developed for single reaction vessels on the new microwave oven were easily transferred to multiple vessels.

The decrease in reaction time was general for a variety of aliphatic amines. However reactions involving amines of reduced nucleophilicity did not proceed to completion. Schultz and co-workers previously reported the use of C-2 fluorinated purines,[19] drawing attention to the nature of the electrophilic partner. The C-2 fluorinated and iodinated analogs **3** and **4**, respectively, were prepared. The fluorinated compound was made similarly to **2**. Alkylation of 2-amino-6-chloropurine with *t*-butyl bromoacetic acid, iodo displacement of the C-2 amine,[20] and cleavage of the *t*-butyl ester under acidic conditions furnished the iodinated compound **4**.[21] Both **3** and **4** were coupled to the resin as before.

Each of the resins **5** was tested in one of the more challenging cases. It was discovered that the nature of the C-6 substituent governed the lability of the C-2 halogen. Electron-rich C-6 susbstituents (e.g., piperidinyl) rendered the purine ring less susceptible to nucleophilic attack while electron-poor substituents reversed the trend. Each of the three resins was treated with piperidine to give **8**. Then each was treated with diethanolamine (an amine that reacted sluggishly) under microwave irradiation to a level that delivered partial conversion to **9**. The conversion levels indicated that both fluoro and iodo substituents were better choices than chloro as the C-2 halogen. Additional studies indicated that the iodo analog produced higher levels of conversion than fluoro (I > F > Cl, Table 1). The finished 2,6,9-trisubstituted purines were cleaved from the resin under standard conditions (TFA:water 95:5).

As a result of this investigation, a collection of trisubstituted 2-(2,6-purin-9-yl)acetamides was produced. Purities for these molecules are typically greater than 75% and isolated yields range from 30% to 80%.[22]

Table 1. Effect of halogen substitution on amine displacement under microwave irradiation



C-2 Halogen	Microwave power (W)	Time	Ratio **9**:**8**
Cl	720	30 min	0.042
F	720	30 min	0.19
I	720	30 min	0.29
F	960	1 h	1.6
I	960	1 h	11

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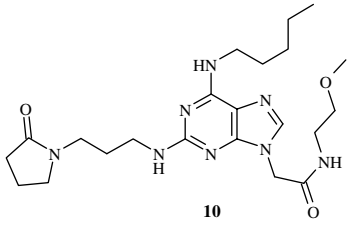
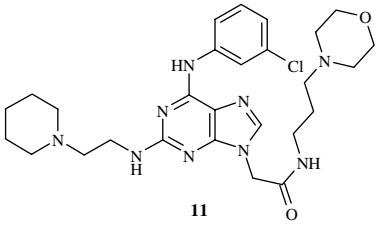
21. **4**: ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.58 (s, 1H), 5.10 (s, 2H).
22. Examples. Compound **10**: ^{1}H NMR (300 MHz, MeOH-d_4): δ 7.67 (s, 1H), 4.77 (d, 2H), 3.53–3.30 (m, 15H), 2.37 (t, 2H, J = 8.0 Hz), 2.02 (m, 2H), 1.83 (m, 2H), 1.66 (m, 2H), 1.40–1.28 (m, 4H), 0.93 (t, 3H, J = 6.9 Hz). Compound **11**: ^{1}H NMR (300 MHz, MeOH-d_4): δ 8.12 (s, 1H), 7.79 (s, 1H), 7.60 (d, 1H, J = 7.6 Hz), 7.27 (m, 1H), 7.01 (m, 1H), 4.78 (s, 2H), 3.67–3.56 (m, 6H), 3.26 (m, 2H), 2.64–2.33 (m, 12H), 1.76–1.60 (m, 6H), 1.47 (m, 2H).



10



11