Tetrahedron Letters 51 (2010) 3174–3176

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

High yielding microwave-assisted synthesis of 2-(arylmethyl)amino-4-arylamino-6-alkyl-1,3,5-triazines

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ARTICLE INFO

Article history:
Received 25 February 2010
Revised 8 April 2010
Accepted 9 April 2010
Available online 14 April 2010

Keywords:
2-(Arylmethyl)amino-4-arylamino-6-alkyl-1,3,5-triazines
Microwave synthesis
Cyclocondensation

ABSTRACT

An efficient and practical procedure was developed to prepare novel 2-(arylmethyl)amino-4-arylamino-6-alkyl-1,3,5-triazines, starting from dicyandiamide and the corresponding arylamines under microwave irradiation and its scope is demonstrated with a number of examples. The valuable feature of this procedure included the short reaction times, high yields, and easy operation.

N-4,6-Disubstituted 1,3,5-triazine-4,6-diamines analogues have been often reported as important core structures in many chemotherapeutic agents, including anti-angiogenesis,[1] depressants for reticuloendothelial hyperfunction,[2] herbicides,[3] antimicrobials,[4] antivirals,[5] antitumors,[6] antimalarials,[7] estrogen receptor modulators[8] and cyclin-dependent kinase inhibitors.[9] Previous synthetic methods for such compounds mainly relied on two approaches. One starts with cyanuric chloride, that is, 2,4,6-trichloro-1,3,5-triazine. Each chloride atom of cyanuric chloride can be substituted by various nucleophiles in the presence of a base. Therefore, a careful control of the temperature during the substitution reactions could allow the synthesis of 2,4,6-trisubstituted-triazines by sequential and selective addition of amines, alcohols, thiols or alkyls.[10,11] However, alkyl replacement can be problematic due to the highly reactive nature of the Grignard reagents. The second involves the formation of triazinic ring, one of which is carried out by the reaction of the amidines, prepared from the corresponding acetonitrile by the procedure of Garigipati[12] and the isourea partners.[13] A limitation of this method was that the latter are often obtained in modest yields. The other ring formation involves the condensation of substituted biguanides with acid chlorides,[14] anhydrides[15] or carboxylates.[16] These reactions are often performed in alcoholic solution in the presence of a strong base. Unfortunately, these transformations have traditionally suffered from long reaction times and modest yields.

In the recent decades, microwave (MW) irradiation has taken an incontestable place in organic synthesis as a very effective and non-polluting method of activation. The scope of applications is very extended and successful, that concerns a wide spectrum of organic syntheses including, for instance, heterocyclic, organometallic, radio, photo reactions, and combinatorial chemistries.[17–19] The main benefits of performing reactions under MW irradiation conditions are the significant rate-enhancements that result in short reaction time, energy saving, and the higher product yields by lowering decomposition of the reagents and/or products and by equilibrating reaction, with displacement by vaporization of light molecules.

In this Letter, we describe a three-step synthesis of 2-(arylmethyl)amino-4-arylamino-6-alkyl-1,3,5-triazines **3a–d** (Scheme 1) using MW techniques. We have focused our efforts on the application of MW irradiation in the cyclocondensation of substituted biguanides with esters, which is a key step for this synthesis.

Our study began with the synthesis of 3,4,5-trimethoxyphenylbiguanide hydrochloride **1a** as precursors of 2-amino-4-(3′4′5′-trimethoxyphenyl)amino-6-alkyl-1,3,5-triazines **2a–c**, from dicyandiamide and 3,4,5-trimethoxyaniline in the presence of hydrochloric acid. The preparation was performed in dioxane under MW irradiation at 90 °C in 15 min.[20] The hydrochloride salts of the 3,4,5-trimethoxyphenylbiguanide were crystallized from the reaction mixture in good yields (89%) and in high purity, and they can be deprotonated with methanolic sodium methoxide in nearly quantitative yield. The other 1-arylbiguanide hydrochlorides **1b–c** can be also obtained from dicyandiamide and commercially available arylamine in the same way (86–87% yields).

The formation of *N*-4-substituted 1,3,5-triazine-2,4-diamine analogues by condensation between biguanides and esters is well

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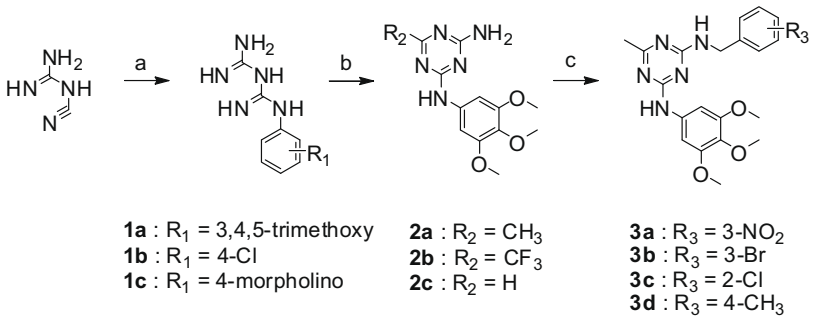
doi:10.1016/j.tetlet.2010.04.042



Scheme 1. Reagents and conditions: (a) arylamine/dioxane/MW, 90 °C, 15 min; (b) R_2CO_2Et/MeONa/THF/MW, 70 °C, 20 min; (c) $ArCH_2Br$/tBuONa/dioxane/MW, 90 °C, 15 min.

known.[16] We believed that we could also implement a MW strategy to enhance the rate of these often slow reactions. In order to optimize the reaction conditions, initially, the effect of heating modes was studied. In our first experiment, condensation between 3,4,5-trimethoxyphenylbiguanide hydrochloride **1a** (1 equiv) and ethyl acetate (3 equiv) in methanolic sodium methoxide (1.5 equiv) was chosen as a prototype to furnish 2-amino-4-(3′,4′,5′-trimethoxyphenyl)amino-6-methyl-1,3,5-triazine **2a**.[21] Reaction times as long as 24 h were necessary under conventional thermal heating conditions and the yield of the desired product was 50%. No amelioration for the yields was observed under the same experimental conditions when the reaction was carried out by using NaOtBu or $NaNH_2$ or KOH as a base, by which **2a** was obtained in 44%, 22% and 15% yield, respectively.

Interestingly, a remarkable rate acceleration was observed in methanolic sodium methoxide under the MW conditions. The reaction was achieved within 20 min at the same temperature, to give the corresponding **2a** in 61% yield (Table 1). It demonstrated the beneficial effect of microwaves as the energy source.

Next, the effect of the solvent was examined and the results are summarized in Table 1. With the exception of entry 1, the yield was very high in most solvents, and the best recovery was recorded in THF.[22] This result could be related to the presence of 'superheating effect',[23] because THF possesses a stronger effect than MeOH. For this reason, THF couples better with MV irradiation, resulting in a higher temperature increase. In a similar manner and using THF as a solvent, **2b**[24] was obtained from **1a** and ethyl trifluoroacetate in quantitative yield and **2c**[25] in 90% from **1a** and ethyl formate.

At last, 2-(arylmethyl)amino-4-arylamino-6-alkyl-1,3,5-triazines **3a**–**d** were prepared by a similar strategy, that is, treatment of **2a** with appropriate derived benzylbromides under MW irradiation in the presence of *t*BuONa as a base and dioxane as a solvent. The MW assisted direct conversion of **2a** was carried out at 90 °C in 10–15 min to afford the expected products **3a**,[26] **3b**,[27] **3c**,[28] and **3d**[29] in 82%, 77%, 69%, and 81% yields, respectively.[30] As these nucleophilic substitution reactions were carried out probably in an S_N1 process, the difference of yields for **3b**–**d**, except **3a** could be quite consistent with the stability of arylmethyl cation intermediates.

Table 1
Solvent influence under MW conditions on reaction rate and yield for the preparation of triazine **2a**

Entry	Solvent	Time (min)	Yield[a] (%)	HPLC[b] (%)
1	MeOH	20	61	99
2	*n*-BuOH	20	97	98
3	Dioxane	20	99	98
4	Acetonitrile	20	99	99
5	THF	20	100	99
6	DMF	5	95	98

[a] Isolated yield of pure compound.
[b] Purity was determined by HPLC at 214 nm.

In conclusion, an efficient, convenient, and practical preparation of novel 2-(arylmethyl)amino-4-arylamino-6-alkyl-1,3,5-triazines, starting from easily accessible dicyandiamide and arylamines in three steps has been carried out under microwave irradiation in high yields. These procedures can be classified as a green synthesis due to short reaction times, reduction of the solvent volume, good yields, and simple work-up procedure. Furthermore, the advantage of this route of synthesis is its application to parallel synthesis that permits an easy and rapid access to a large number of derivatives for biological evaluation as potential chemotherapeutic agents.

Acknowledgment

We thank Le Corre Laurent for the use of microwave reactor and Mauro Hélène for the mass spectra recording.

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20. All MV reactions were performed in a BenchMate monomode reactor (IR detector for temperature) from CEM corporation.
General procedure: A mixture of dicyandiamide (10.8 mmol, 1 equiv), arylamine (10.8 mmol, 1 equiv), and concentrated HCl (10.8 mmol, 1 equiv) in dioxane (20 ml) was introduced into a 50 mL round-bottomed flask equipped with a condenser and a magnetic stirring bar. The flask was placed in the microwave cavity and subjected to microwave irradiation for 15 min at 90 °C using irradiation power of 150 W. After cooling to room temperature, the arylbiguanide hydrochloride salt was precipitated. The solid was collected by filtration, washed with dioxane.
21. Compound **2a**: ^{1}H NMR (250 MHz, DMSO-d_6) δ: 2.18 (3H, s), 3.61 (3H, s), 3.75 (6H, s), 6.92 (2H, s, br), 7.20 (2H, s), 9.29 (1H, s). MS (ESI) m/z 292.1 (M+1).
22. *General procedure*: A mixture of sodium methoxide (0.75 mmol, 1.5 equiv) prepared from Na and methanol, arylbiguanide hydrochloride (0.5 mmol, 1 equiv), and ethyl acetate (1.5 mmol, 3 equiv) in dry THF (3 ml) was introduced into a 50 mL round-bottomed flask equipped with a condenser and a magnetic stirring bar. The flask was placed in the microwave cavity and exposed to microwave irradiation for 20 min at 70 °C using irradiation power of 100 W. On cooling to room temperature, the mixture was evaporated under vacuum, and the residue was subjected to flash chromatography (silica gel, 5% methanol/CH_2Cl_2) to afford the desired product as a white solid.
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24. Compound **2b**: ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.63 (3H, s), 3.77 (6H, s), 7.17 (2H, s), 7.88 (2H, s, br), 10.04 (1H, s). MS (ESI) m/z 346.1 (M+1).
25. Compound **2c**: ^{1}H NMR (250 MHz, DMSO-d_6) δ: 3.62 (3H, s), 3.76 (6H, s), 7.12 (2H, s), 7.16 (2H, s), 8.14 (1H, s), 9.36 (1H, s). MS (ESI) m/z 278.1 (M+1).
26. Compound **3a**: ^{1}H NMR (250 MHz, DMSO-d_6) δ: 2.14 (3H, s), 3.64 (3H, s), 3.68 (6H, s), 5.29 (2H, s), 6.55 (2H, s), 6.92 (2H, s), 7.60 (1H, t, J = 8 Hz), 7.75 (1H, d, J = 8 Hz), 8.15 (2H, m). MS (ESI) m/z 427.1 (M+1).
27. Compound **3b**: ^{1}H NMR (250 MHz, DMSO-d_6) δ: 2.13 (3H, s), 3.65 (3H, s), 3.67 (6H, s), 5.16 (2H, s), 6.50 (2H, s), 6.89 (2H, s), 7.29 (2H, s), 7.45 (2H, s). MS (ESI) m/z 460.1 (M+1).
28. Compound **3c**: ^{1}H NMR (250 MHz, DMSO-d_6) δ: 2.11 (3H, s), 3.63 (3H, s), 3.67 (6H, s), 5.24 (2H, s), 6.62 (2H, s), 6.88 (2H, s), 7.31 (2H, s), 7.43 (2H, s). MS (ESI) m/z 416.1 (M+1).
29. Compound **3d**: ^{1}H NMR (250 MHz, DMSO-d_6) δ: 2.12 (3H, s), 2.25 (3H, s), 3.64 (9H, s), 5.12 (2H, s), 6.48 (2H, s), 6.84 (2H, s), 7.10 (4H, m). MS (ESI) m/z 396.1 (M+1).
30. *General procedure*: A mixture of 2-amino-4-(3′,4′,5′-trimethoxyphenyl)amino-6-methyl-1,3,5-triazine **2a** (0.17 mmol, 1 equiv), arylmethylbromide (0.19 mmol, 1.1 equiv), and tBuONa (0.26 mmol, 1.5 equiv) in dioxane (2.5 ml) was introduced into a 50 mL round-bottomed flask equipped with a condenser and a magnetic stirring bar. The flask was placed in the microwave cavity and exposed to microwave irradiation for 15 min at 90 °C using irradiation power of 150 W. On cooling to room temperature, the mixture was diluted with CH_2Cl_2, washed with water, and dried over anhydrous Na_2SO_4. The solution was concentrated under vacuum, and the residue was subjected to flash chromatography (silica gel, 5% methanol/CH_2Cl_2) to give the desired product.