Tetrahedron Letters 51 (2010) 5385–5387

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Highly efficient and safe procedure for the synthesis of aryl 1,2,3-triazoles from aromatic amine in a continuous flow reactor

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ARTICLE INFO

Article history:
Received 29 June 2010
Revised 26 July 2010
Accepted 26 July 2010
Available online 1 August 2010

Keywords:
Flow chemistry
Organic azides
Aryl 1,2,3-triazoles
1,3-Cycloaddition

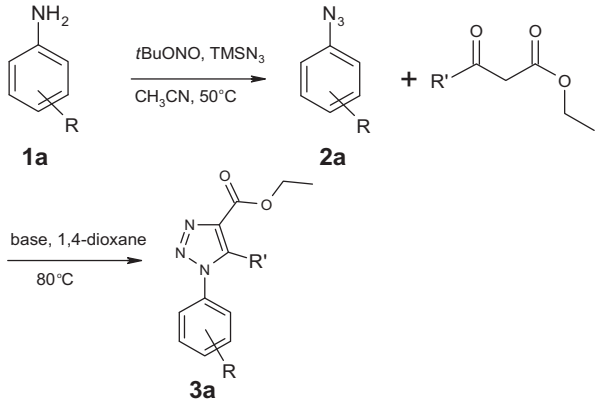
ABSTRACT

The Letter reports a safe and reliable synthesis of aryl 1,2,3-triazoles from the corresponding anilines via intermediate aryl azides, using a continuous process. The method was applied to a variety of substrates with good to excellent yields, without the need to isolate the reactive and possibly unstable intermediates which were constantly kept at low concentration in the matrix environment.

Nowadays, the growing interest of the synthetic community in continuous flow processes is demonstrated by an increase in the numbers of applications that have been recently published.[1] Among the potential advantages over the existing batch processes we would like to mention, for example, the precise control of the reaction variables, the increased safety parameters (only a small amount of reagent is present in the reactor, circumventing engineering issues such as heat and mass transfer), and the capability of readily scaling-up the synthetic procedure by simply adjusting the running period or the flow rate of the reaction coupled with the appropriate reactor size.[2]

The use of organic azides raises safety concerns since organic azides are well known to be heat and shock-sensitive compounds and also sensitive to traces of strong acids and metallic salts which may catalyze explosive decomposition.[3] In addition to this, they are routinely prepared from the corresponding amines[4] via their diazonium salts, raising, once more, the safety concerns associated with these reactive intermediates.[5] Among the few methods available, we focussed our attention on that involving the use of stable and non-explosive reagents, such as *tert*-butylnitrite (*t*-BuONO) and azidotrimethylsilane ($TMSN_3$) in acetonitrile, under anhydrous conditions.[6] Several mechanistic studies demonstrated that the reaction doesn't proceed via diazonium salt, but via a triazene intermediate, which is subsequently nitrosylated and finally converted to an aryl radical.[7] Besides the high reactivity of all the reaction intermediates and the nitrogen evolution, heating a reaction involving radical species necessitates accurate thermal hazard considerations. A continuous flow method for the formation and use, in situ, of the highly reactive intermediate species and final azides, could represent a very attractive improvement. The reactive species are used immediately after their formation, so that the local concentration of the hazardous intermediate (triazene, alkyl radical and azide products) is always very low.

In this Letter, we disclose a less hazardous and practical synthesis of aryl azides from their corresponding amine and their direct application in the synthesis of 1,2,3-triazoles, using a continuous flow process.[8] The reaction equation is shown in Scheme 1.



Scheme 1. Two step 1,2,3-triazoles synthesis.

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doi:10.1016/j.tetlet.2010.07.149

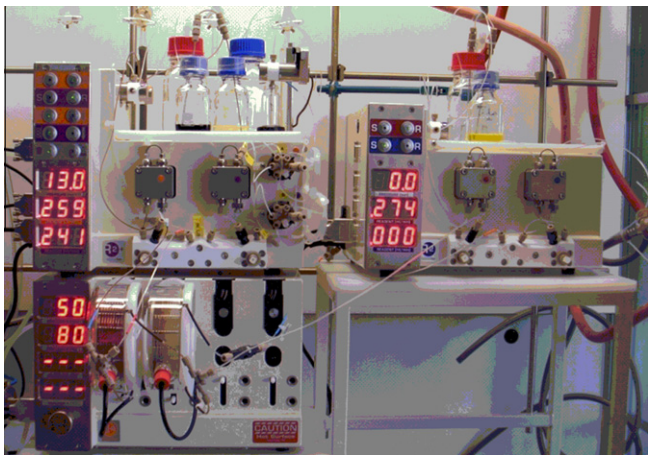

Figure 1. Vapourtec R2/R2+/R4 flow system.

As indicated, the aryl azide is synthesized with *t*-BuONO and $TMSN_3$ in acetonitrile, and then reacted with the enolate, generated from various β-ketoester derivatives in the presence of a base.[9]

We conducted the flow experiments using the commercially available synthesis platform, Vapourtec R2/R2+/R4 system,[10] shown in Figure 1. The main R2+ system is composed of two integrated HPLC pumps: the flow rates could be regulated and set at any value between 0.01 ml and 10 ml min^{-1}, working with a system pressure of up to 30 bar (ca. 435 psi). We included an additional R2 system composed of two supplementary HPLC pumps, to be given the possibility of using up to four reagents/solvents. The mixing of the reagents' streams is achieved with a simple T-piece and the combined output was directed, through perfluoroalkoxy tubing, to the convection-flow coil (CFC) which can be heated up to 150 °C. The R4 heater guarantees precise temperature control in four independent heating zones with rapid temperature ramping and cooling. The addition of a back pressure regulator (up to 250 psi) is usually applied in-line, allowing access to higher temperature while avoiding solvent boil over. At the top, a large drip tray is located for reagent bottles and collection vessels. The reaction conditions were first tested and optimized in a batch mode, using *p*-bromoaniline as a model substrate. The first step showed complete conversion via NMR after as long as 20 min: a solution of *t*-BuONO (1.5 equiv) in acetonitrile was added to a solution of aniline (1 equiv) and $TMSN_3$ (1.2 equiv) in acetonitrile (exothermic addition), and heated at 50 °C. The second step proved to be more problematic: a solution of ethyl isopropylacetoacetate and EtONa in EtOH was added to the solution resulting from the previous step and heated at 60 °C. Despite observing the complete consumption of the intermediate aryl azide after 30 min, we ended up with a mixture of the desired product and the corresponding acid precipitating out of the solution. This adverse event made the reaction inapplicable in the flow system, because it would lead to a blockage of tubes.

Thus, we decided to further optimize the reaction conditions including a screening of temperature (ranging from 60 to 80 °C), solvent (EtOH, CH_3OH, acetonitrile, 1,4-dioxane), and bases (EtONa, tBuOK, TEA and DBU) in the presence of ethyl isopropylacetoacetate. Superior conditions to be applied to the flow system were

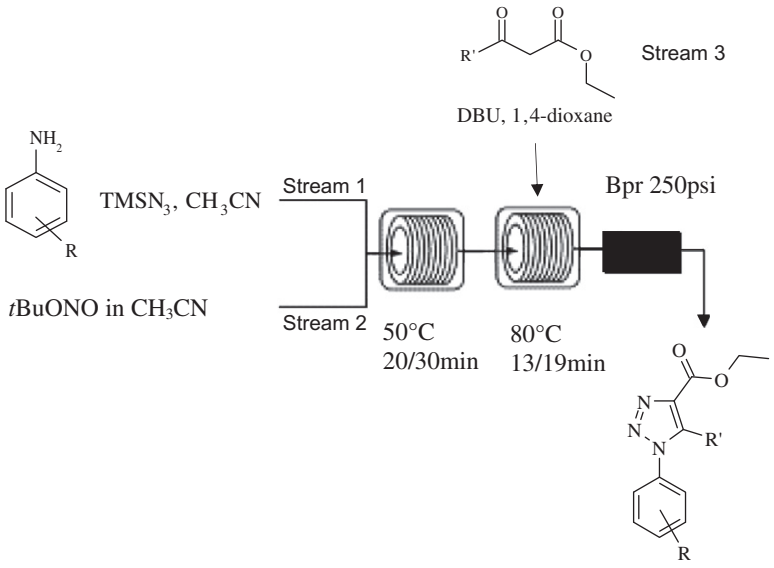

Figure 2. Reaction set-up for flow process.

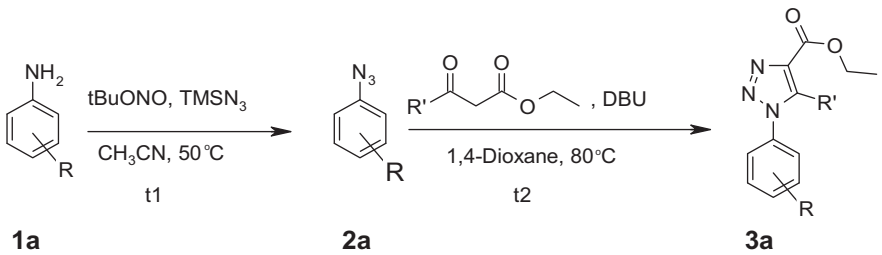

Figure 3. General synthetic scheme.

Table 1
Synthesis of various 1,2,3-aryltriazoles in a continuous flow reactor[12]

Entry	R	R′	t_1[a] (min)	t_2[b] (min)	Product	Yield (%)
1	4-Br	*i*Pr	20	13	**3a**	72
2	4-MeO	*i*Pr	30	19	**3b**	59
3	3-CN	*i*Pr	20	13	**3c**	57
4	4-CF_3	*i*Pr	20	13	**3d**	65
5	4-COOEt	*i*Pr	20	13	**3e**	79
6	4-COMe	*i*Pr	20	13	**3f**	70
7	4-CF_3	Ph	20	13	**3g**	74
8	4-CF_3	CF_3	30	19	**3h**	68
9	4-CF_3	*t*Bu	30	19	**3i**	54

[a] t_1: residence time reactor 1.
[b] t_2: residence time reactor 2.

achieved with DBU and 1,4-dioxane at 80 °C. After as little as 10 min, the reaction was complete, without solid formation. Figure 2 depicts the instrument set-up to carry out the process in the flow system.

Stream 1, containing $TMSN_3$ in acetonitrile and Stream 2, containing the aniline in acetonitrile, were mixed through a T-piece and flowed into the first loop reactor, with an internal volume of 10 ml, pre-heated at 50 °C. The reactor output was mixed to Stream 3, the β-ketoester and DBU solution in 1,4-dioxane and flowed into a second loop reactor with an internal volume of 10 ml pre-heated to 80 °C. The system was fitted with a back pressure regulator (Bpr) of 250 psi. The collected stream was quenched with a saturated solution of NH_4Cl, ready for the work-up procedure. After extraction and purification by flash chromatography, the 1,2,3-triazoles were isolated (Fig. 3). Taking advantage of some initial trials, the flows were adjusted in order to have a residence time of 20–30 min in the first reactor (arylazide formation). Consequently, the second residence time resulted in being between 13 min and 19 min.[11] These reactor set-ups were deemed necessary in the light of the variable reaction time for the second step.

We ascribed this variability to the ring substitution: anilines with electron-donating groups (EDG) needed a residence time almost double for the cyclization step. In fact, the cyclization reaction implied, at first, the β-ketoester enolate attack to the azide in a way that the starting electron-rich anilines corresponded to a slightly lower reactivity than electron-poor anilines (entries 2 and 3).

We were delighted to find out that the cycloaddition step was completely regioselective and the yields of the products were good to excellent, considering they were calculated on isolated products over two steps (Table 1). We extended the substitution pattern of the desired triazoles, by reacting the 4-CF_3-aniline with differently substituted acetoacetate (entries 7–9): in the case of ethyl trifluoroacetoacetate and ethyl *tert*-butylacetoacetate the second step took longer, probably for either electronic or steric effects.

In conclusion, we set up a reliable procedure for a two steps-synthesis of aryl 1,2,3-triazoles from the corresponding anilines in continuous flow. The tight control of the reaction variables combined with the advantages offered by the continuous flow application for the reaction scale-up, made this process of undoubted synthetic utility.

Acknowledgment

We gratefully acknowledge Ornella Curcuruto (Analytical Chemistry) for the support given in the MS analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.149.

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10. Vapourtec R2+/R2/R4 units are available from Vapourtec Ltd, Place Farm, Ingham, Suffolk IP31 1NQ UK. Web site: http://www.vapourtec.co.uk.
11. Reactions were first tried on a batch mode to determine the residence time for the cyclization step. For all the compounds reported in Table 1 the formation of the azide was completed in 20 min. A prolonged reaction time (30 min) had no impact on the purity of the intermediate azide, at least by NMR.
12. See Supplementary data general procedures and compounds' characterization.