Tetrahedron Letters 50 (2009) 1708–1709

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Rapid and easy access to indoles via microwave-assisted Hemetsberger–Knittel synthesis

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ARTICLE INFO

Article history:
Received 19 December 2008
Revised 20 January 2009
Accepted 23 January 2009
Available online 29 January 2009

Keywords:
Indole
Hemetsberger–Knittel
Microwave

ABSTRACT

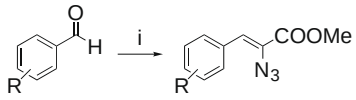
Hemetsberger–Knittel indole synthesis can be carried out under microwave activation. The optimum reaction conditions were found by using different solvents and by varying irradiation times and temperature. After 10 min of microwave irradiation, high conversion into the corresponding indole products was achieved without formation of any side products.

Indole derivatives display a wide range of biological activities as exemplified by the amino acid tryptophan, the hormones serotonin and melatonin, the anti-inflammatory drug indomethacin, the psychotropic drug LSD and the anti-tumour agent vinblastine.[1] Accordingly, the synthesis of indole derivatives has been a major topic in organic and medicinal chemistry over the past several decades.[2] For over 100 years, the Fischer indole synthesis has been one of the most used methods for the preparation of indoles.[3] However, the Fischer indole synthesis suffers from the shortcomings of low yields and numerous side products.[4]

In our design of kinase inhibitors, we were interested in different substituted indole-2-carboxylates. Although a multitude of methods exist for the synthesis of these compounds, they afford only relatively low to modest yields. The Hemetsberger–Knittel indole synthesis involves the condensation between an arylaldehyde and an azidoacetate to provide α-azidocinnamates which upon heating give indoles. The process has been applied using high boiling solvents such as xylene[5], toluene,[6] and mesitylene and a reaction time of approximately 4 h to obtain the corresponding indoles and a variety of aromatic N-heterocycles in yields between 53% and 79%. Recently, Stokes et al. described a mild procedure for the ring closure using rhodium(II) perfluorobutyrate as catalyst and an extended reaction time of 16 h.[7] We present here a rapid and simple method using 10 min microwave irradiation to synthesize different indole-2-carboxylates in good yields.

The synthesis begins with recently described[7] preparation of the intermediates **1** from the corresponding commercially available aldehydes as shown in Scheme 1. The ring closing reaction (Scheme 2) to form the indoles **2** was carried out in a microwave oven (MW).

To ascertain the optimal reaction conditions to form the indoles, different solvents were tested. An initial attempt with **1f** in toluene with microwave irradiation for 15 min at 200 °C and a pressure of 8.1 bar gave a full conversion to the corresponding indole. In a further step, we used more polar solvents at the same conditions with a high total acid number (TAN) δ value, which should improve the conversion of the electromagnetic energy into heat. As outlined in Figure 1, ethanol and 1-butanol were poorer solvents compared to toluene, as indicated by the lower yields of indoles and the presence of many side products. Dioxane takes an intermediate position. The indole was formed in a comparatively good yield, but various side products were also formed. To determine whether the high conversion rate in the presence of toluene depends on its high boiling point or the reaction proceeds better in non-polar solvents, we used *n*-hexane under the same reaction conditions. Like toluene, *n*-hexane gave full conversion (Fig. 1). In view of the fact that the indoles that were obtained crystallized out in the presence of *n*-hexane, we chose this particular solvent for optimizing irradiation exposure and temperature.



1a-f

Scheme 1. Synthesis of α-azidocinnamates. Reagents and conditions: (i) methyl 2-azidoacetate, NaOMe, −20 °C, 4 h.

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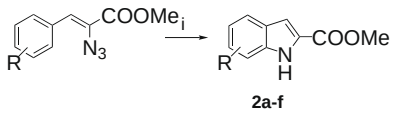
doi:10.1016/j.tetlet.2009.01.129



2a-f

Scheme 2. Synthesis of indole-2-carboxylates. Reagents and conditions: (i) MW, *n*-hexane, 200 °C, 10 min, 15 bar.

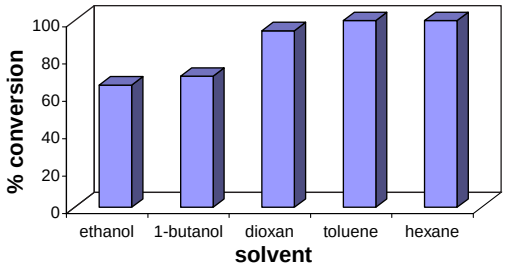


Figure 1. The effect of different solvents on the % conversion to indoles.

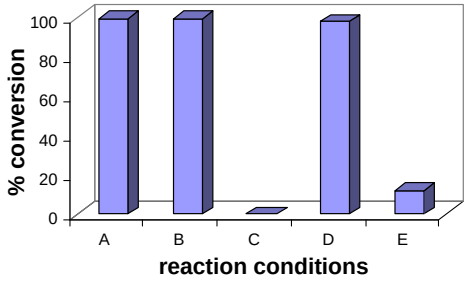
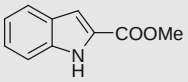
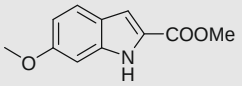
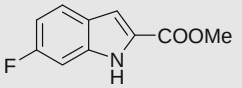
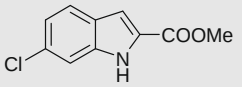
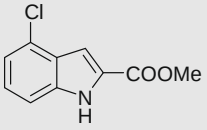
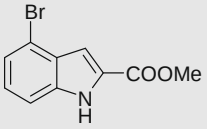


Figure 2. The effect of reaction conditions on the % conversion to indoles. (A) 200 °C, 15 min, 13.5 bar. (B) 200 °C, 10 min, 13.5 bar. (C) 200 °C (only 136 °C were reached), 5 min, 6.2 bar. (D) 150 °C, 10 min, 6.9 bar. (E) 100 °C, 10 min, 4.2 bar.

As shown in Figure 2A, formation of indoles took place with 99.9% yield as indicated by HPLC at 200 W, 200 °C and 15 min irradiation time, and thereby achieved 13.5 bar in *n*-hexane. When we reduced only the reaction time to 10 min, we still achieved a quantitative conversion (Fig. 2B), but irradiation for only 5 min (C) gave no product.

Perhaps the yield was reduced because a temperature of only 136 °C was attained in this short reaction time. Next, we limited the temperature to 150 °C (D) and 100 °C (E), but maintained 10 min microwave activation time. A reaction temperature of 150 °C resulted in 97.9% conversion (D), but essentially no transformation to the indole occurred at lower temperature (E). Pressure was not a determinant factor in all reactions, but it was not allowed to exceed 15 bar. Different values of pressure were achieved, depending on the different given temperatures as well as on irradiation times.

Table 1
Synthesis of indole-2-carboxylates

Compound	Product	Conversion
2a		94%
2b		90%
2c		Quantitative
2d		89%
2e		Quantitative
2f		Quantitative

Ultimately, we selected the conditions 200 W, 200 °C and 10 min MW irradiation time as the standard method to synthesize all indole-2-carboxylates **(2a–f)** outlined in Table 1. Excellent conversions to the indole products were attained in all cases.

In summary, we have developed a convenient microwave-assisted, economical and fast method for synthesis of indole-2-carboxylates. This method can be easily adapted for ring closure of all previously described α-azidocinnamates and therefore provides an easy and rapid access to different substituted indoles and a variety of aromatic N-heterocycles.

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