Ketonitriles as Intermediates for the Synthesis of Antiparasitic Drugs

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Abstract

Objective: Synthesize β-ketonitriles as intermediates towards an effective drug to counteract the parasitic tropical disease leishmaniasis.

Introduction: Diaminopyrimidines have been used as drugs against parasitic diseases like malaria, and less notably against leishmaniasis. Increased resistance, decreased efficacy, and severe side effects have been observed in the current treatment regimen highlighting the need for new drugs against those diseases.

Methods: Six esters reacted with four different nitriles in the presence of potassium tert-butoxide using tetrahydrofuran as solvent to form β-ketonitriles.

Results: Twenty-four β-ketonitriles were synthesized using a microwave reactor, with yields varying from 30 to 72%.

Conclusion: Microwave conditions are appropriate for the synthesis of β-ketonitriles. Yields were variable, with starting materials containing amino groups resulting in lower yields of solid compounds of difficult purification.

Introduction

Leishmaniasis is a disease transmitted by sand flies in tropical areas of the world and affects approximately 15 million people. The current treatments for leishmaniasis are lengthy, prone to dangerous adverse effects and not easily available in the poorest areas where the disease thrives. *Leishmania*, like most organisms, depends on the folate pathway for its survival. However, antifolate drugs do not show significant effect against the parasite because of the existence of an alternative pathway called pteridine reductase 1 (PTR1 – Figure 1). Diaminopyrimidines, which can be prepared from β-ketonitriles, have the potential to inhibit both DHFR and PTR1, killing the parasite (2).

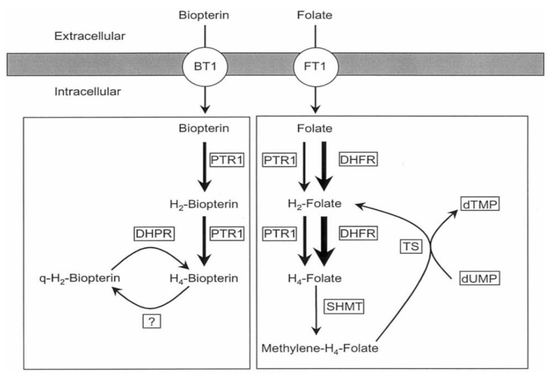


Figure 1. Pteridine salvage in *Leishmania*

Methods

Esters **1a** to **1f** were dissolved in anhydrous tetrahydrofuran. Nitriles **2a** to **2d** and potassium tert-butoxide were added and the mixture, contained in 10 mL vials, was heated in a microwave reactor for ten minutes to produce twenty-four β-ketonitriles (3). The reactions were quenched with a dilute solution of hydrochloric acid, diluted with ethyl acetate and washed in separatory funnels with water. The aqueous phase was extracted with 2 x 50 mL of ethyl acetate. The organic phase was dried over sodium sulfate, filtered, and concentrated through rotary evaporation. The β-ketonitriles were purified through flash chromatography and concentrated. NMR spectra (^{1}H and ^{13}C) of representative compounds is presented in figure 3. 4-(4-isobutylphenyl)-3-oxo-2-phenethylpentanenitrile (**3b**) was prepared from a racemic mixture of the methyl ester of ibuprofen (2-(4-isobutylphenyl) propanoic acid). No attempt was made to purify the enantiomers.

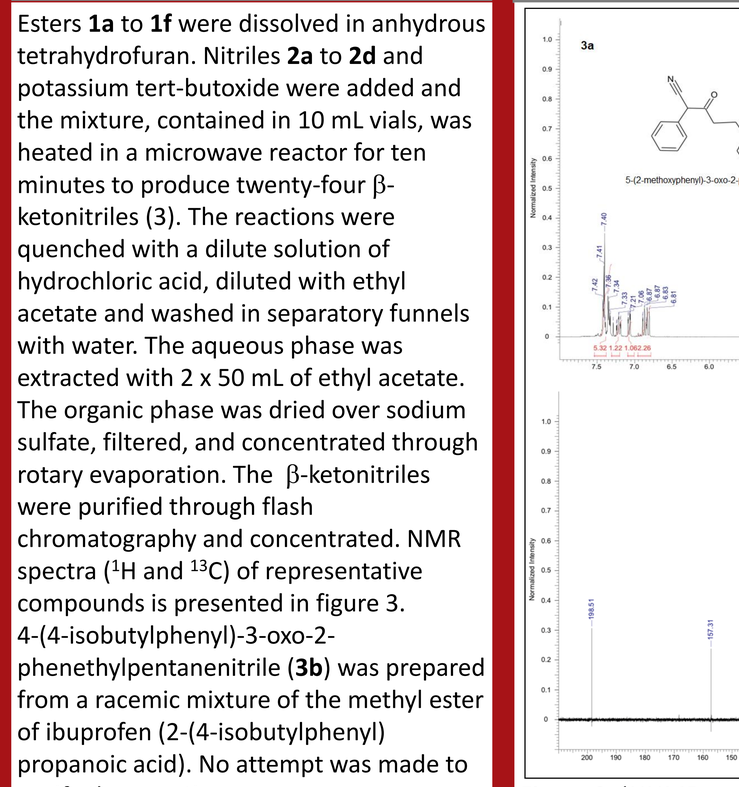
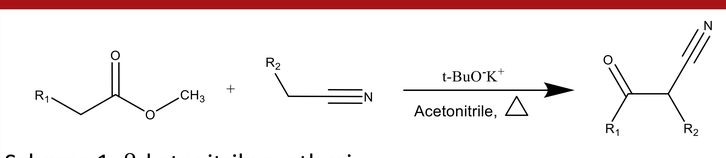


Figure 3. ^{1}HNMR and ^{13}CNMR of representative compounds 5-(2-methoxyphenyl)-3-oxo-2-phenylpentanenitrile (3a) and 4-(4-isobutylphenyl)-3-oxo-2-phenylpentanenitrile (3b).



Scheme 1. β-ketonitrile synthesis.

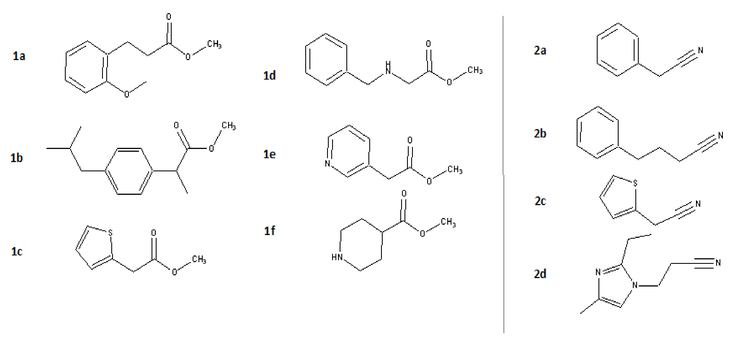


Table 1. Esters and nitriles used to make the β-ketonitriles.

Conclusions

Microwave conditions are appropriate for the synthesis of β-ketonitriles. Yields varied from 30 to 72%. Starting materials containing amino groups resulted in lower yields probably due to competition with the carbanion for the nucleophilic attack to the carbonyl group. The solid compounds obtained were of difficult purification. Compounds obtained from hydrocarbonic starting materials gave better yields and were easier to purify.

References

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