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Synthesis of 1-(3-Chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione V.1

In 1 collection

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Manuscript citation:
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Protocol status: Working
We use this protocol and it's working

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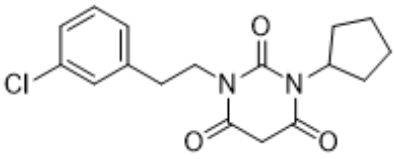
Abstract

1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione (8), is a potent and highly selective Ca(V)1.3 L-type calcium channel antagonist. This protocol is an adaption of Kang *et al.* 2012 's method of the synthesis of this chemical.



1-(3-Chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione

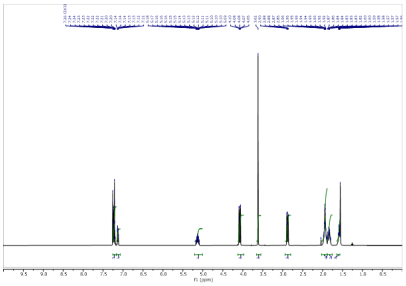
Guidelines

All solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Water was purified by an Elix® UV-10 system. In vacuo refers to the use of a rotary evaporator attached to a diaphragm pump.
Thin layer chromatography was performed on aluminium plates coated with 60 F254 silica.

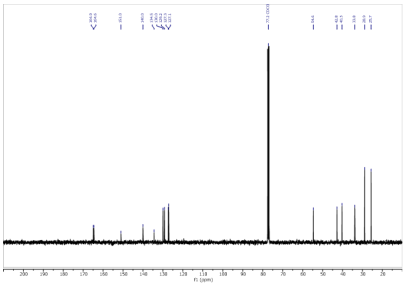
Plates were visualised using UV light (254 nm) or 1% aq. KMnO4. Flash column chromatography was performed on Kieselgel 60M silica in a glass column.

NMR spectra were recorded on Bruker Avance spectrometers (AVIII 400) in the deuterated solvent stated. The field was locked by external referencing to the relevant deuteron resonance. Chemical shifts (d) are reported in parts per million (ppm) referenced to the solvent peak. 1H spectra reported to two decimal places, and 13C spectra reported to one decimal place, and coupling constants (J) are quoted in Hz (reported to one decimal place). The multiplicity of each signal is indicated by: s (singlet); br. s (broad singlet); d (doublet); t (triplet); q (quartet); dd (doublet of doublets); td (triplet of doublets); qt (quartet of triplets); or m (multiplet).

Low-resolution mass spectra were recorded on an Agilent 6120 spectrometer from solutions of MeOH.



NMR spectra (1)



NMR spectra (2)

Materials

Equipment:
Agilent 6120
Elix UV-10 system
Bruker Avance spectrometers (AVIII 400)

Reagents:
Aluminum Plates Coated in F254 Silica
Kiesegel 60M Silica

2-(3-chlorophenyl)ethylamine (2.58 mmol, 1.0 eq)
cyclopentaneisocyanate (2.58 mmol, 1.0 eq)
CH_2Cl_2
Malonyl chloride (2.84 mmol, 1.1 eq)

Synthesis of 1-(3-Chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-(1H,3H,5H)-trione

1 Add **357 µL** 2-(3-chlorophenyl)ethylamine (2.58 mmol, 1.0 eq.) to a solution of 290 mg of Cyclopentaneisocyanate (2.58 mmol, 1.0 eq.) in 10 mL of CH_2Cl_2.

2 Stir at RT for **5 h**

3 Monitor completion with Low-Resolution Mass Spectrometry

4 Add **276 µL** Malonyl chloride (2.84 mmol, 1.1 eq.) **dropwise** under vigorous stirring **over 5 min**.

5 Stir mixture for **1 h** and concentrate in vacuo.

6 Purify residue by column chromatography on silica gel (EtOAc/pentane, 1:4), product should be a white solid (687 mg, 80%)

7 Check data is comparable with the the literature:

NMR: H NMR (400 MHz, CDCl3) δ 7.25 – 7.19 (m, 3H), 7.13 (dt, J = 6.7, 2.1 Hz, 1H), 5.20 – 5.07 (m, 1H), 4.13 – 4.03 (m, 2H), 3.62 (s, 2H), 2.92 – 2.84 (m, 2H), 1.94 (tqd, J = 8.0, 4.9, 2.0 Hz, 4H), 1.89 – 1.79 (m, 2H), 1.61 – 1.57 (m, 2H); 13C NMR (101 MHz, CDCl3) δ 164.9, 164.6, 151.1, 140.0, 134.5, 123.0, 129.2, 127.3, 127.1, 54.6, 42.8, 40.3, 33.8, 28.8, 25.7; LRMS m/z (ESI^-) 333.1 $[M-H]^-$.

Protocol references

Kang, S.; Cooper, G.; Dunne, S. F.; Dusel, B.; Luan, C.-H.; Surmeier, D. J.; Silverman, R. B. CaV1.3-selective L-type calcium channel antagonists as potential new therapeutics for Parkinson's disease. Nature Communications 2012, 3 (1), 1146. DOI: 10.1038/ncomms2149.