Multicomponent synthesis of tertiary alkylamines by photocatalytic olefin-hydroaminoalkylation

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Tertiary alkylamines found in ~25% top 200 best selling drugs

GSK4112 obesity
Neupro muscular skeletal disorder
ANAEXX-73 Alzheimer’s

Traditional disconnections

State-of-the-art approaches

Existing photoredox methods for α-amino radical formation

Arylation
oxidation to radical cation
Zyvox (linezolid) antibiotic

Alkylation
direct H-atom abstraction
Fluoxetine (Prozac) anti-depressant

oxygen radical
decarboxylation
Lyrica (pregabalin) precursor anti-convulsant

Challenge: selective formation of unfunctionalized α-amino radical is difficult via existing photoredox methods

Design Plan: Photocatalytic SET of iminium ions

In(III) photocatalyst

α-amino radical

alkyl radical

Hydroamination

amine-carbonyl condensation

SET

Hantzsch ester

reaction complete in <2 hours

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Proposed mechanism for photocatalytic iminium alkylation

Redox-Relay of iminium ions

Photocatalytic SET of iminium ions

ir(ppy)3 (oxidant)

Ir(ppy)3 (reductant)

oxidation

red

SET

Hantzsch ester

iminium ion

radical addition

direct HAT (not observed)

HEH (observed)

40 W blue lamp

Deuterium-labelling studies

Irp(ppy)3 (1 mol%)

Hantzsch ester (1.5 equiv.)

propionic acid (20 mol%)

65% (1:1 dr)

66%

80% (2:1:1 dr)

References:

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