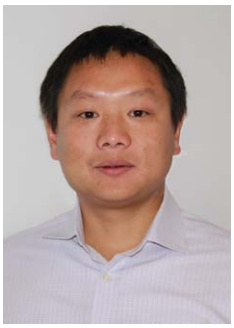
SYNLETT

Spotlight 451

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

N,*N*-Dimethylaniline (NNDMA)

Compiled by Chao Huang



Chao Huang was born in Hubei, P. R. of China, and studied medicinal chemistry at Yunnan University, receiving his M.Sc. degree in 2009. Subsequently, he started his doctoral work under the supervision of Professor Jun Lin at the same university. His research interests focus on the development of new synthetic methodologies and on the synthesis of heterocycles of medicinal interest.

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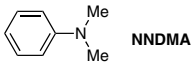
Introduction

N,*N*-Dimethylaniline (NNDMA, CAS: 121-69-7, Scheme 1) is colorless liquid with a boiling point of 193–194 °C. It is a simple but widely applied reagent. It is not only used as a starting material in the synthesis of dyestuffs, pharmaceuticals, agrochemicals, and fine chemicals, but also used as a solvent, stabilizer, and analytical reagent.[1] The low price of NNDMA (due to the industrial production) has played an important role for its applications.

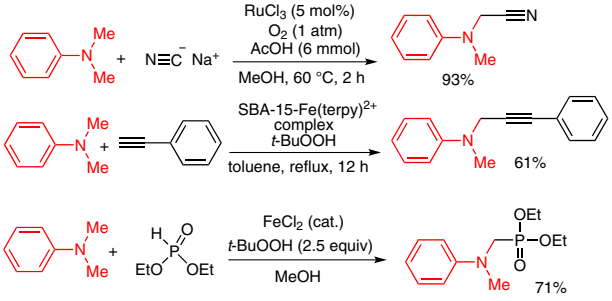


Scheme 1

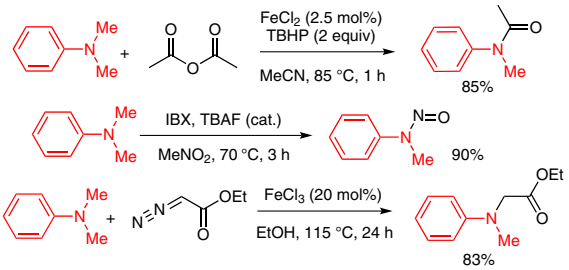
In its original applications, NNDMA was used as a solvent, in electrophilic substitutions on the *para*-position of the benzene ring, and to prepare quaternary amines. However, in recent years, researchers have paid more and more attention to developing further applications, such as the reactions on the methyl groups attached to the nitrogen atom. According to the literature published in the last years, NNDMA can react with alkenes, alkynes, active methylenes, and cyano groups. By C–C and C–N bond activation of NNDMA, nitrogen compounds can be constructed with reagents containing active hydrogens, and NNDMA can be used to prepare heterocyclic compounds by coupling reactions.

Abstracts

(A) *Activation of C–H Bond in N–Me:*
Using metal catalysts and oxidants, the C–H bond of the *N*–Me group of NNDMA can be activated and replaced by an unsaturated compound like an alkene,[2] alkyne,[3] CN,[4,5] C=N,[6] and active methylene.[5,7] There are two *N*-Me groups on NNDMA, but a single C–H bond activation is much easier. With the above reaction, the intermediate compounds are obtained in high yield under mild conditions. Iron(II), copper(I), ruthenium, and iridium metal salts are usually used as the catalysts, and *tert*-butyl hydroperoxide (TBHP) or O_2 is used as the oxidant. The C–H bond in *N*-Me is activated, and the hydrogen atom can be replaced by peroxide, alcohol[8] and phosphoric acid ester groups.[9]



(B) *Activation of N–C Bond in N–Me:*
By C–N bond cleavage, amide, *N*-nitrosamines and other nitrogen-containing compounds can be prepared under mild conditions in high yield. The methyl group can be replaced by an acetyl group with $FeCl_2$ and *tert*-butyl hydroperoxide,[10] and it can be replaced by NO with *o*-iodoxybenzoic acid (IBX), nitromethane, and R_4NX (X = halide).[11] With diazoacetate and $FeCl_3$, the methyl group can be replaced by an acetate group.[12] Cytochrome P450 enzymes can achieve demethylation of NNDMA.[13]



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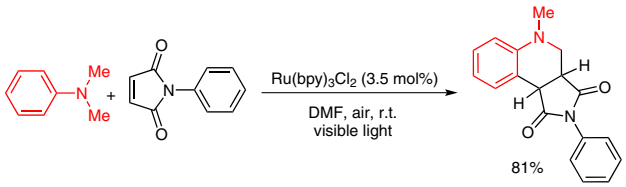
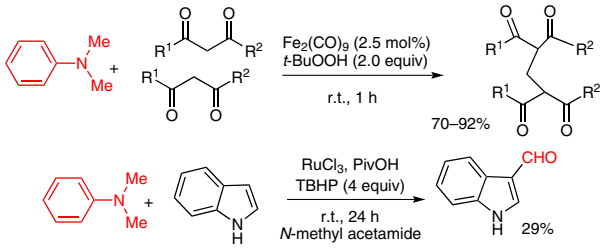
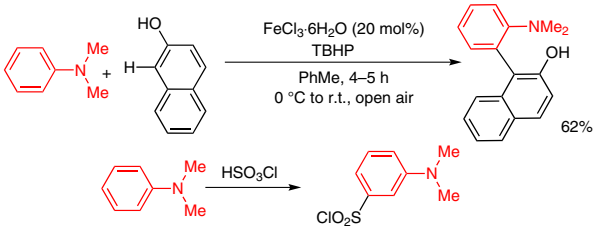
(C) *Cyclization Reactions:*
Tetrahydroquinolines can be prepared using $Ru(bpy)_3Cl_2$ or CuBr as the catalyst and air or TBHP as the terminal oxidant.[14–16] But, to the best of our knowledge, all products obtained are racemates.



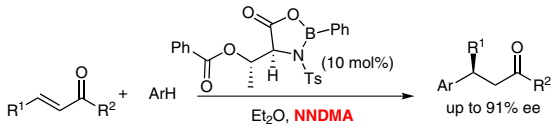
(D) *Donation of a One-Carbon Unit:*
NNDMA can donate a one-carbon unit after catalysis and oxidation with iron. The reaction can be used to prepare bis-1,3-dicarbonyl derivatives.[17] NNDMA was also a carbonyl source in the mild and selective ruthenium-catalyzed formylation of indoles.[18]



(E) *Susbtitutions on the Benzene Ring:*
Regioselective reactions of NNDMA in the *ortho*, *meta*, and *para* positions on the benzene ring can be realized. The regioselective, catalyzed cross-dehydrogenative coupling (CDC) usually proceeds on the *ortho* or *para* position of the benzene ring,[19] and sulfurochloridic acid can react with the *meta* position to prepare 4′-substituted compounds having 5-HT6 receptor affinity.[20,21] In addition, the benzene ring of NNDMA can be reduced by NHC-stabilized ruthenium nanoparticles (RuNPs) to prepare (partial) hydrogenation products.[22]



(F) *Other Special Uses:*
Used as solvent or reaction additive, NNDMA can stimulate the enantioselectivity Friedel–Crafts alkylation of furans and indoles.[23] Moreover, it can donate NMe_2 groups[24] and promote *ortho* lithiation of anilines by formation of quaternary ammonium salts.[25]



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