Tetrahedron Letters 57 (2016) 5695–5699

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Pd-catalyzed domino reactions of nitroaromatics: A surrogate access towards the saturated *N*-heterocycles

Nagaraju Vodnala [a], Dhananjaya Kaldhi [a], Saibabu Polina [b], V.P. Rama Kishore Putta [b], Richa Gupta [a], S.C. Pinky Promily [a], R.K. Linthoinganbi [a], Virender Singh [c], Chandi C. Malakar [a,*]

[a] Department of Chemistry, National Institute of Technology Manipur, Imphal 795004, Manipur, India
[b] Department of Medicinal Chemistry, Jubilant Biosys, Bangalore 560022, Karnataka, India
[c] Department of Chemistry, National Institute of Technology Jalandhar, Jalandhar 144011, Punjab, India

ARTICLE INFO

Article history:
Received 15 August 2016
Revised 5 November 2016
Accepted 7 November 2016
Available online 9 November 2016

Keywords:
N-Heterocycles
Reductive cyclization
Domino reaction
Pd-catalysis
Nitroaromatics

ABSTRACT

Using Pd/HCOOCs as a surrogate reagents synthesis of saturated *N*-heterocycles was described from nitroaromatics as starting materials. The developed new reaction conditions exclude the generally used toxic reagents like carbon monoxide as deoxygenative agent. The developed protocol permits the synthesis privileged bioactive *N*-heterocyclic scaffolds in good yields and selectivity.

In recent years synthesis of heterocycles gained considerable impact in the field of medicinal chemistry due to their occurrence in a broad range of biologically active compounds and in marketed drug molecules.[1–3] Among the heterocyclic scaffolds, the preparation of saturated *N*-heterocycles have emerged considerable attention due to their solitary chemical, biological and pharmacological properties.[4,5] Their unique chemical and pharmacological profile inspired chemist towards novel syntheses of saturated *N*-heterocycles.[4,5] Abundance of these key structural motifs in naturally occurring bioactive compounds as well as in pharmaceuticals alleges a sound impact to admit them into an important class of compounds (Fig. 1).[4,5] Hence, during the recent years the development of mild and atom economy methods for the synthesis of *N*-heterocycles with distinct substitution motifs has emerged as a field of augmenting points of pursuit in organic synthesis.[1–5] Among the devoted efforts towards the synthesis of saturated *N*-heterocycles a broad range of traditional protocols involving the formation of C-N bonds have been dedicated. The most useful, straightforward and widely explored approaches for the preparation of saturated *N*-heterocycles refers to the reductive cyclization of nitroaromatics, nucleophilic substitution and dipolar cycloaddition reaction.[4–6] Miserably, myriad of these methods often agonizes from limitations such as the use of a large excess of deoxygenative agents and drastic reaction conditions.[4–6] Interestingly, a collection of surrogate methods based on the palladium-catalyzed C—N bond formation have also been evolved in the past years to serve this purpose.[4a,6j] Among the saturated *N*-heterocycles 1,4-benzothiazines, 1,4-benzoxazines and tetrahydroquinolines scaffolds received considerable attention to chemist.[6h–j] In this regards, last few years literature witnessed an enormous amounts of work for their synthesis using ω-nitroalkenes as easy available starting materials and the key step of the reactions hinged upon reductive cyclization of nitroaromatics.[6h–j] However, most importantly the previously presented methods rely on the use of excess P(III) reagents and molecular carbon monoxide as deoxygenative agents leading to the formation of the corresponding oxides in the first case. Both excess P(III) reagents as well as its corresponding oxides remains difficult to remove from the reaction mixtures. On the other hand, the use of highly toxic carbon monoxide molecule as deoxygenative agent hampers the application of this method. Nevertheless, the early report towards the synthesis of 1,4-bezoxazines and tetrahydroquinolines associated with the use of excess triethyl phosphite as deoxygenative agent that suffers from the unavoidable limitation due to the formation of considerable amounts of corresponding *N*-ethylated side products.[6h,i] The limitation of the parent report associated with the formation of side product was repaired using

* Corresponding author.
E-mail address: chdeepm@gmail.com (C.C. Malakar).

http://dx.doi.org/10.1016/j.tetlet.2016.11.037
0040-4039/

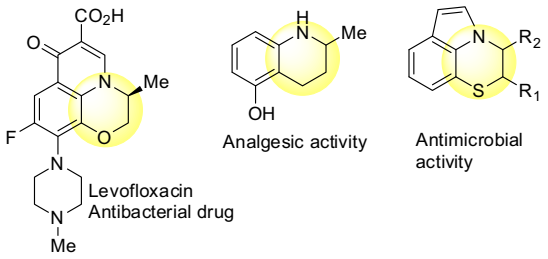
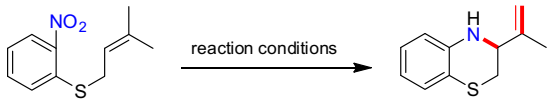


Figure 1. Selected examples of saturated *N*-heterocycles.

reaction of ω-nitroalkenes in presence of Mo(VI) as catalyst and triphenylphosphine as deoxygenative agent.[7] Unfortunately, the use of P(III) reagents still remains a major drawbacks of the existing reported protocols towards the synthesis of these structural motifs. Therefore, the development of a novel method that excludes the use of P(III) reagents to achieve the synthesis of saturated *N*-heterocycles is highly desired. Having extensively reviewed the reported works associated with the preparation of saturated *N*-heterocycles starting from nitroaromatics, we focused on exploring this transformation using ω-nitroalkenes as substrate since these classes of compounds are very seldom studied under Pd-catalyzed transformation.[6j] Additionally, the current work targeted on developing surrogate transformation of ω-nitroalkenes to saturated *N*-heterocycles avoiding the use of P(III) reagents. Hence, in order to achieve this purpose ω-nitroalkenes were used as model substrates and a mixture of Pd-catalyst in presence of Lewis acid, and cesium formate (HCOOCs) as reducing agent were explored as reaction conditions. A careful literature study revealed that there is still no report on the reductive cyclization of nitroaromatics using a mixture of Pd-catalyst and cesium formate as reagents. In context, a plethora of other reagents have been investigated towards the reductive cyclization of nitroaromatics.[1–6] Here we disclose a mild and efficient synthetic protocol for the preparation of 1,4-benzothiazines, 1,4-benzoxazines and tetrahydroquinolines using ω-nitroalkenes as cheap starting material based on easy to operate domino reaction.

To begin with the preliminary screening of reaction conditions the starting ω-nitroalkenes were prepared using the previously reported methods.[6h,i,7] The starting material 2-nitrophenyl thioether **1a** was considered as a model substrate and interestingly, a reaction of **1a** in presence of 0.05 equiv. of $PdCl_2$ as catalyst and 3 equivs. of HCOOCs as reducing agent in DMF as solvent at 120 °C for 16 h in sealed vial afforded the desired 3-isopropenyl-3,4-dihydro-2*H*-1,4-benzo-thiazines **2a** (Table 1, entry 1). In order to investigate the detailed and efficient reaction conditions for the effective conversion of **1a** to **2a**, next the reactions were carried out in the presence of 0.05 equiv. of $PdCl_2$ as catalyst, 0.15 equiv. of an additive and 3 equivs. of HCOOCs as reducing agent in DMF as solvent at 120 °C for 16 h in sealed vial (Table 1, entries 2–11). Among the additives applied during the optimization studies (Table 1, entries 2–11), it was observed that $SnCl_2$ revealed the highest efficacy towards the transformation of **1a** to **2a** with the isolated yield of 31% (Table 1, entry 8). Moreover, additives such as $MoCl_5$, $FeCl_3$, TfOH and AcOH were proved to be not suitable for this transformation leading to the formation of complex mixture of compounds (Table 1, entries 4 and 9–11). It was also observed that the use of surrogate reducing agent delivered unsatisfactory results

Table 1
Preliminary screening of the reaction conditions for the transformation of **1a** to **2a**.[a]



1a **2a**

Entry	Conditions	**2a**, Yield%
1	$PdCl_2$ (0.05 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	9[b]
2	$PdCl_2$ (0.05 equiv.), $ZnCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	15[b]
3	$PdCl_2$ (0.05 equiv.), $TiCl_4$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	6[b]
4	$PdCl_2$ (0.05 equiv.), $MoCl_5$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
5	$PdCl_2$ (0.05 equiv.), $CuCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	19[b]
6	$PdCl_2$ (0.05 equiv.), $In(OTf)_3$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	17[b]
7	$PdCl_2$ (0.05 equiv.), $Yb(OTf)_3$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	14[b]
8	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	31[b]
9	$PdCl_2$ (0.05 equiv.), $FeCl_3$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
10	$PdCl_2$ (0.05 equiv.), TfOH (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
11	$PdCl_2$ (0.05 equiv.), AcOH (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
12	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), $HCOONH_4$ (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
13	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOONa (3 equiv.), DMF, 120 °C, 16 h, sealed tube	5[b]
14	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOK (3 equiv.), DMF, 120 °C, 16 h, sealed tube	9 [b]
15	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOH (3 equiv.), DMF, 120 °C, 16 h, sealed tube	Complex mixture[c]
16	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.10 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	26 [b]
17	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.05 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	15 [b]
18	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOCs (2 equiv.), DMF, 120 °C, 16 h, sealed tube	19 [b]
19	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), HCOOCs (1 equiv.), DMF, 120 °C, 16 h, sealed tube	8 [b]
20	$SnCl_2$ (0.15 equiv.), HCOOCs (3 equiv.), DMF, 120 °C, 16 h, sealed tube	-[d,b]
21	$PdCl_2$ (0.05 equiv.), $SnCl_2$ (0.15 equiv.), DMF, 120 °C, 16 h, sealed tube	- [d,b]

[a] Unless otherwise indicated, all reactions were performed using **1a** (1 mmol) in dry DMF (2 mL) under mentioned conditions.
[b] Starting material recovered.
[c] Complex mixture observed on TLC which was not purified.
[d] Cleavage of the starting material was observed.