

Unexpected Side Reaction in the Intermolecular N-H Insertion of Phenyl Diazoacetates with Arylamines

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Abstract: Unexpected side reaction is discovered from the N-H insertion of phenyl diazoacetates with arylamines in the presence of $\text{Rh}_2(\text{OAc})_4$ catalyst. This side reaction is not evident with copper catalysts such as $\text{Cu}(\text{acac})_2$ or $\text{Cu}(\text{OTf})_2$. Good yield of the N-H insertion was obtained by using 0.2% of copper catalyst.

Keywords: N-H insertion, diazoester, carbene, ylide, rearrangement.

Phenyl α -amino acids, as part of the unnatural α -amino acids, are key intermediates of many natural products. Limited synthetic approaches towards phenyl α -amino acids have been reported¹. Transition metal catalyzed N-H insertion of phenyl diazoacetate with amines can be a straightforward method towards this end. However, only few examples of such N-H insertion approach were documented in literature^{2,3}. In our continuing efforts of application of metal carbenoid chemistry in the synthesis of biologically active compounds, we turned to be interested into processing this chemistry. In our study, we found an unexpected side reaction involved in the N-H insertion with rhodium catalyst (**Scheme 1**).

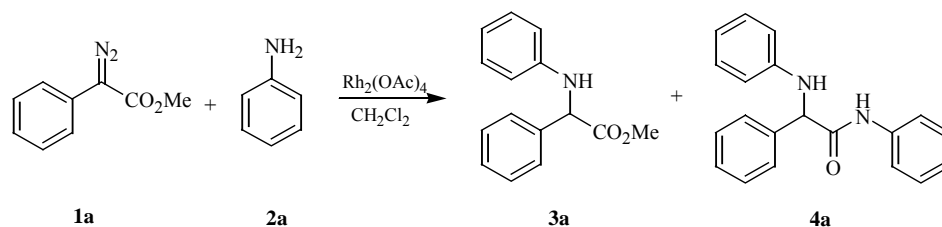
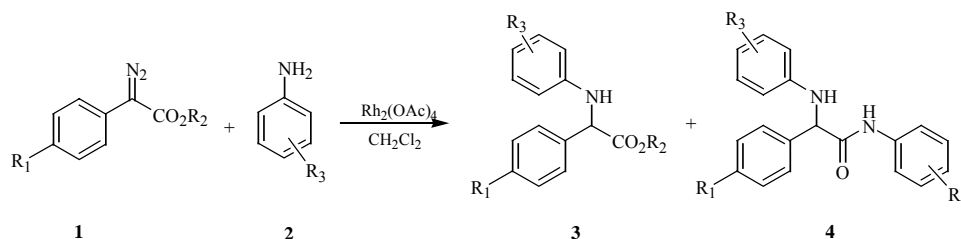
Treatment of methyl phenyl diazoacetate **1a** with aniline **2a** in the presence of 1% rhodium acetate gave N-H insertion product **3a** in 69% yield⁴. To our surprise, unexpected side reaction occurred to give α -amino phenylacetamide **4a** in 8% yield, and product **4a** was not resulted from aminolysis of **3a** with excess aniline. No reaction occurred by treatment of amino acid product **3a** with aniline **2a** under the same reaction as conducted for diazo decomposition.

To get better understanding of this side reaction, various phenyl diazoacetates **1** and anilines **2** were employed. Formation of the side product α -amino phenylacetamide was found to be quite general and results are summarized in **Table 1**.

As can be seen from the **Table**, there is a weak trend of the electronic effect of aniline substitution on the selectivity. Electron-donating substitution gave less side product (entry a-e). The reverse was true for the substitution on the phenyl ring of the diazo compounds. Less side product was found with electron withdrawing substitution

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Scheme 1

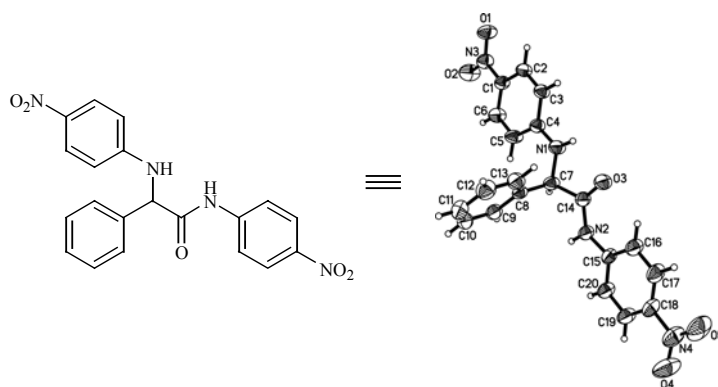
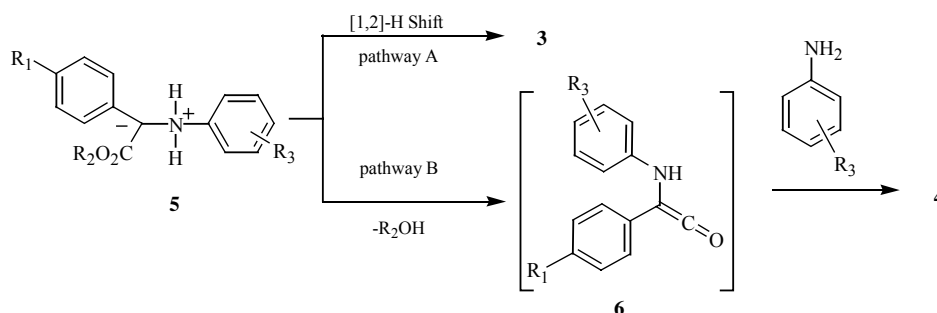
Table 1 Rhodium catalyzed N-H insertion of phenyl diazoacetates with anilines^a

Entry	R ₁	R ₂	R ₃	Yield(%) ^b	3:4 ^c
a	H	CH ₃	H	77	90:10
b	H	CH ₃	<i>o</i> -CH ₃ O	75	92:8
c	H	CH ₃	<i>p</i> -F	74	89:11
d	H	CH ₃	<i>p</i> -CF ₃	61	80:20
e	H	CH ₃	<i>p</i> -NO ₂	68	86:14
f	OCH ₃	CH ₃	H	91	91:9
g	Cl	CH ₃	H	93	96:4
h	NO ₂	CH ₃	H	79	100:0
i	H	CH ₂ Ph	H	68	89:11
j	H	CH ₂ -CH=CH ₂	H	90	85:15
k	H	Ph	H	80	73:27
l	H	CH(CH ₃) ₂	H	77	72:28
m	H	^t Bu	H	88	62:38

^aReaction conditions see ref 4. ^bIsolated yield of **3** and **4** after column chromatography purification.

^cDetermined by ¹H-NMR from crude reaction mixture.

(entry f-h). For instance, *para*-nitro substituted phenyl diazoacetate gave essentially no side product (entry h). Further investigation indicated that the ester group of phenyl diazoacetate also had significant effect on the selectivity (entry i-m). More sterically hindered ester group gave higher percentage of the side product. Structure of the side product was further confirmed by single crystal X-ray of **4e** (Figure 1)⁵.

Figure 1 Perspective view of X-ray structure of **4e****Scheme 2**

The situation for metal carbenoid insertion into N-H bonds is not very clear now. And a generally accepted pathway for the N-H insertion is through a metal free ylide intermediate **5** (Scheme 2, pathway A)⁶. Although it is unclear for the formation the side product **4**, one possible reaction pathway is proposed here. In competition with the 1,2-proton shift from ylide intermediate **5** to give N-H insertion product, loss of an alcohol could result ketene intermediate **6**. Instantly trapping of the ketene intermediate by aniline forms side product **4** (pathway B). Nucleophilicity of carbon anion of ylide **5** was reported to form C-C bond in our recently publication⁷, which could be rationalized as a driving force for the ketene intermediate **6** formation.

For comparison, copper catalysts were also employed to investigate this N-H insertion process. We were surprised to find that no such side reaction occurred with either Cu(acac)₂ or Cu(OTf)₂.

N-H insertion of phenyl diazoacetate **1a** with arylamine **2a** was further studied by lowering catalyst loading. With Cu(OTf)₂ loading as low as 0.2%, N-H insertion product **3a** was obtained in 61% yield.

In conclusion, unexpected side reaction is reported in the rhodium catalyzed N-H insertion of phenyl diazoacetates with arylamines. This side reaction did not occur with copper catalyst. Possible mechanism is proposed.

Acknowledgments

We are grateful for financial support from the Chinese Academy of Sciences and National Nature Science Foundation of China (20202011). We thank Prof. Kaibai Yu of Chengdu Institute of Organic Chemistry for X-ray measurement.

References and Notes

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4. General procedure: A solution of diazoester (1.0 mmol) in 5 ml of CH₂Cl₂ was added to CH₂Cl₂ (10 ml) solution of Rh₂(OAc)₄ (4.4 mg, 0.01 mmol) and arylamine (1.2 mmol) *via* a syringe pump (5 ml/h) during 1 hour. After completing addition, the reaction mixture was cooled to room temperature. Solvent was moved under reduced pressure. Crude product was subject to ¹H-NMR to determine product ratio, and which was further purified by column chromatography to give product **3** and **4**.
5. Crystal data for **4e**: (a) Monoclinic, space group P2(1)/c, a = 6.833(1) Å, b = 16.775(3) Å, c = 16.456(2) Å, V = 1886.3(5) Å³, Z = 4, ρ_{calcd} = 1.382 Mg/m³, F(000) = 816, λ = 0.71073 Å, T = 296(2) K, μ(Mo Kα) = 1.382 Mg/m⁻¹. Data for the structure were collected on a Siemens P-4X four-circle diffractometer. Intensity measurements were performed on a crystal (dimensions 0.50 x 0.46 x 0.28 mm) in the range 1.73 <2θ<25.50°. (b) CCDC- 228396 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge *via* www.ccdc.cam.ac.uk.
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Received 9 February, 2004