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A New Approach to Prepare 2-Acetyl-Mono (5,6,7,8)-Nitro-1,2,3,4-Tetrahydroisoquinolines

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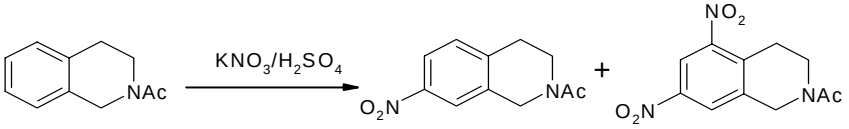
Abstract: N-Acetyl-*p*, *m* or *o*-nitro-phenylethylamines and $(HCHO)_n$ were treated in 60% H_2SO_4/HOAc, *via* α-amidoalkylation to give 2-acetyl-mono(5, 6, 7 or 8)-nitro-1,2,3,4-tetrahydro-isoquinolines. Additionally, some interesting phenomena were observed when the comparison between 2-acetyl-5, 6, 7 or 8-nitro-1,2,3,4-tetrahydroisoquinolines and 2-alkylsulfonyl-5 , 6 or 7-nitro-1,2,3,4-tetrahydroisoquinolines was made.

Keywords: α-Amidoalkylation, 2-acetyl-mono (5, 6, 7, 8)-nitro-1,2,3,4-tetrahydroisoquinolines, nitro-1,2,3,4-tetrahydroisoquinolines.

2-Acetyl-nitro-1,2,3,4-tetrahydroisoquinolines are very important intermediates for organic synthesis[1]. McCoubrey reported 2-acetyl-7-nitro-1,2,3,4-tetrahydro-isoqunoline and 2-acetyl-5,7-dinitro-1,2,3,4-tetrahydroisoqunoline could be prepared by nitration of 2-acetyl-1,2,3,4-tetrahydroisoquinoline, low yield and tiresome purification procedure were disadvantages of this method , and 2-acetyl-5, 6 or 8-nitro-1,2,3,4-tetrahydro-isoquinolines could not be obtained according to this approach (**Scheme 1**)[2,3,4].

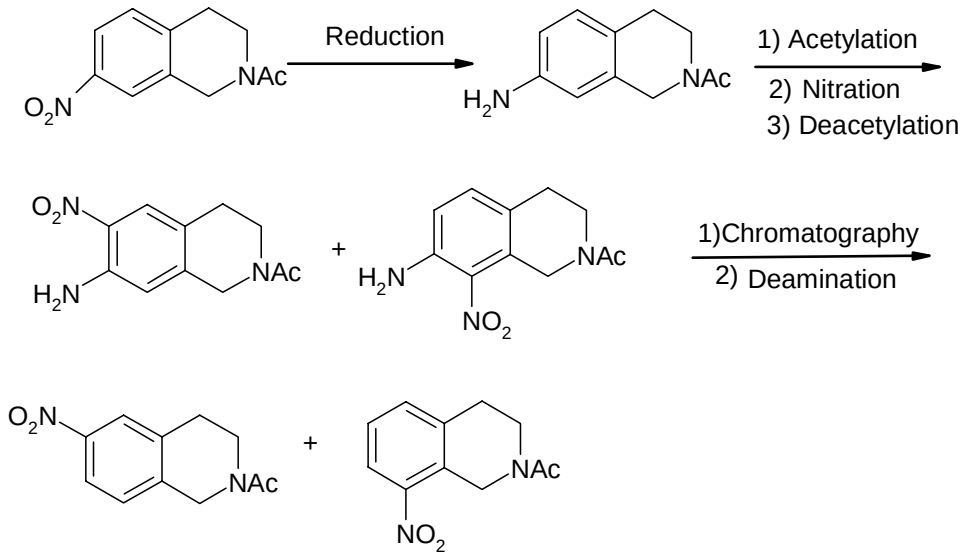
Scheme 1



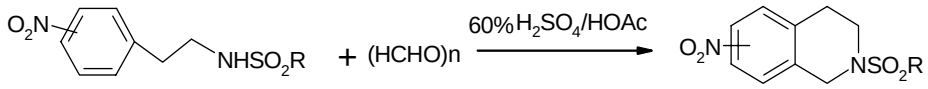
The method of preparation of 2-acetyl- 6 or 8-nitro-1,2,3,4-tetrahydroisoquinolines was reported by Tercel , but this method also was limited to be used widely due to the low yields and tiresome chromatography separation (**Scheme 2**)[5]. In 1998, Quallich reported one multi-step approach to prepare tetrahydroisoquinolines with electron withdrawing group, but the reagents and material was expensive for used widely[8]. In 1996, Stokker reported N-trifluoroacetyl-*p*-nitro-phenyl-ethylamine could be converted into 2-trifluoroacetyl-7-nitro-1,2,3,4-tetrahydro-isoquinoline[6]. Previously, we reported that the reaction of N-methyl-sulfonyl-*p* or *m* or *o*-nitro-phenylethylamine with $(HCHO)_n$ in 60% H_2SO_4/HOAc gave 2-methylsulfonyl-mono(5,6 ,7)-

nitro-1,2,3,4-tetrahydroisoquinolines. However, 8- nitro-1,2,3,4-tetrahydroisoquinoline could not be obtained in this case (**Scheme 3**)[7].

Scheme 2



Scheme 3



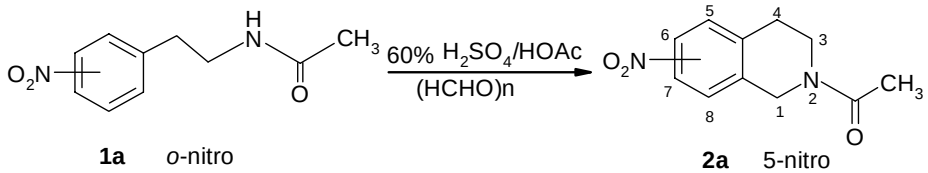
Now, we would like to report a new approach to prepare 2-acetyl- mono (5, 6, 7, 8)-nitro-1,2,3,4-tetrahydroisoquinolines with much more cheap material N-acetyl- *p*, *m* or *o*-nitro-phenylethylamines *via* α -amidoalkylation reaction .The position of nitro did not play an important role in the conversion , but the reaction temperature could influence the speed of reaction significantly, the favorable temperature was 40-50℃ (**Scheme 4**).

In the procedure of experiments, interesting phenomena occurred. Contrast to our previous report [7], when N-acetyl-*m*-nitro-phenylethylamine was treated with paraform in 60% H_2SO_4/HOAc, both 2- acetyl-6-nitro-1,2,3,4-tetrahydroisoquinoline and 2-acetyl-8-nitro-1,2,3,4-tetrahydroisoquinoline were produced. They could be separated by silica chromatography[5].

^{1}H-NMR data of 2-acetyl-5, 6,7 or 8-nitro-1,2,3,4-tetrahydroisoquinolines showed that two isoformers existed, the ratio of two isoformers was about 3:2, which was similar to the reports of Stokker[5] and Tercel (see ^{1}HNMR data of **2c** in the experiment part)[6]. Contrast to this phenomena, only one isoformer of 2-alkylsulfonyl-mono (5,6,7)–nitro-1,2,3,4-tetrahydroisoquinolines was observed[7]. The possible reason of

these differences is the hindrance of the sulfonyl group.

Scheme 4



1a *o*-nitro
1b *m*-nitro
1c *p*-nitro

2a 5-nitro
2b 6-nitro
8-nitro
2c 7-nitro

Typical cyclization procedure of ***(2c)***: 5.5g (26.6mmol) N-acetyl -*p*-nitro-phenylethyl-amine and cold 60% H_2SO_4/HOAc (v/v) 25 ml were added into 50 ml flask, fine powder $(HCHO)_n$ 1.20g (39.8mmol) was added. The reaction mixture was stirred at 40~50℃ for 8hr. The mixture was cooled to room temperature and poured into 200 ml ice-water under stirring. This resulted mixture was extracted with 50×3 ml CH_2Cl_2 and washed with 20×3 ml H_2O, dried over anhydrous $MgSO_4$. The solvent was evaporated off to give pale solid, which was recrystalized from ethyl acetate or chloroform to give white solid. m.p:84－86℃[1~4]. Yield: 88%, ^{1}H-NMR (300MHz, $CDCl_3$, δ *ppm*): a 3:2 mixture of amide isoformers doubling most signals, 2.20(s,1.8H,CH3), 2.22(s,1.2H,CH3), 2.95(t, J=12Hz, 0.8H,N-CH_2-), 3.02 (t, J=12Hz,1.2H,N-CH_2-), 3.74(t, J=12Hz, 1.2H,Ar-CH_2-), 3.87(t, J=12Hz, 0.8H,Ar-CH_2-), 4.73(s,0.8H, Ar-CH_2-N), 4.80(s,1.2H, Ar-CH_2-N) 7.28-8.07(m,3H, aromatic).

In conclusion, a convenient method for the preparation of 2-acetyl-5, 6 , 7 or 8-nitro-1,2,3,4-tetrahydroisoquinolines from much more cheap material was developed.

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