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REACTIONS OF β-NITROSTYRENES WITH GRIGNARD REAGENTS

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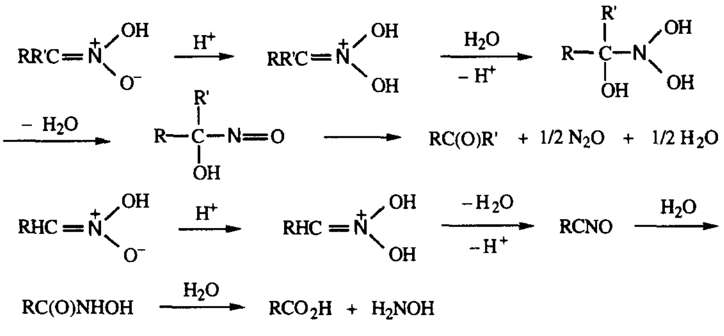
Abstract: α-Phenyl-β-nitrostyrene **1a** and β-nitrostyrene **1b** react with Grignard reagents to generate hydroximoyl halides **3** or nitrile oxides **4** after workup with ice cold concentrated aqueous HX acid solution. Carboxylic acids **5** are the only products isolated from **1b** and products **3** or **4** are still obtained from **1a** when concentrated sulfuric acid solution is used.

Conjugated nitroalkenes are exceptional Michael acceptors to organometallic reagents. When nitroalkenes are added to Grignard reagents, high yields of nitroalkanes, *aci* nitro compounds or carbonyl compounds can be obtained.[1] Nef found that primary or secondary nitro compounds can be hydrolyzed, respectively, to aldehydes or ketones, by treatment of their conjugate bases with sulfuric acid. Primary nitro compounds are converted into carboxylic acids, through the Meyer reaction[2] when treated with concentrated sulfuric acid. Thus, either the Nef or the Meyer reaction occurs when the conjugate base is added to the strong acid (Scheme I).



Scheme I

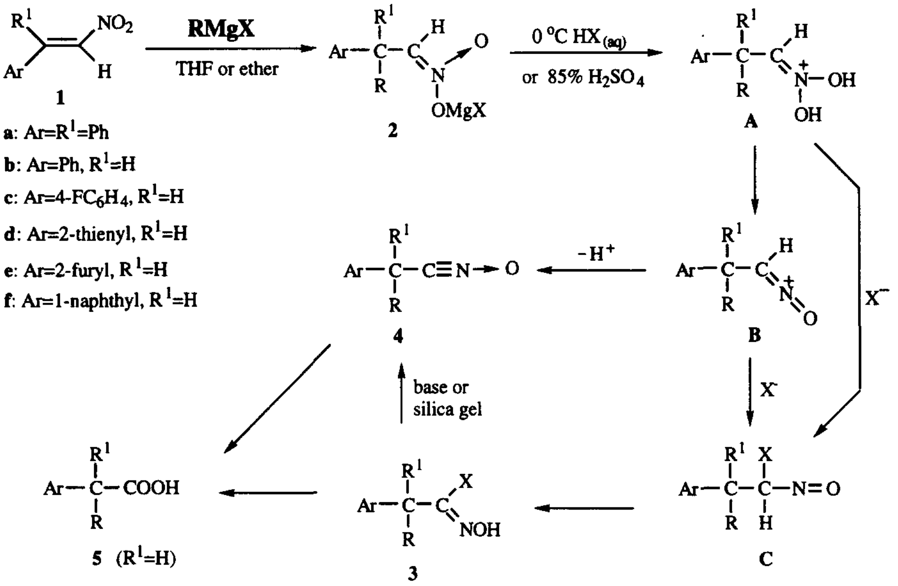
α-Phenyl-β-nitrostyrene **1a** and 2-aryl-1-nitroethenes **1b-1f** react with Grignard reagents under a nitrogen atmosphere to give, via 1,4-addition, *aci*-anions **2**. When *aci*-anions **2** are added to dilute aqueous hydrochloric acid (5%) solution, high yields (60-95%) of nitroalkanes are obtained. On the other hand, the hydroximoyl halides **3** or nitrile oxides **4** are generated when *aci*-anions **2** are added to[3] ice cold concentrated aqueous HX acid solution (HCl 37%, HBr 48%, HI 57%). However, carboxylic acids **5** are the only products isolated from **2b-2f** when 85% H_2SO_4 is used, although compounds **3** and **4** are stable enough to be separated when nitronate **2a** is hydrolyzed in the same condition (Table 1). The generation of different products must be ascribed to steric effect in the *aci*-anion **2** and the presence of good trapping reagents such as halide. In the case of **2a**, the two phenyl groups are presumed to block the attack of the water molecule so that the hydroximoyl halides **3** or nitrile oxides **4** can be isolated. On the other hand, the intermediates **3** and **4** are hydrolyzed to the carboxylic acids **5**

Table 1 The addition of *aci*-anion **2** to concentrated $HX_{(aq)}$ or 85% $H_2SO_{4(aq)}$

				(% yield)		
Entry	nitrostyrene	RMgX	$HX_{(aq)}$	3	4	5
1	1a	$(CH_3)_3CMgCl$	HCl		50	
2	1a	$(CH_3)_2CHMgCl$	HCl	77		
3	1a	$CH_3CH_2CH_2MgCl$	HCl	96		
4	1a	$CH_3CH_2CH_2MgBr$	HBr	93		
5	1a	CH_3MgCl	HCl	82		
6	1a	CH_3MgBr	HBr	85		
7	1a	CH_3MgI	HI	95		
8	1a	$C_6H_5CH_2MgCl$	HCl	95		
9	1a	$C_6H_5CH_2MgCl$	HCl		95*	
10	1a	$C_6H_5CH_2MgBr$	HBr	94		
11	1a	$c\text{-}C_6H_{11}MgBr$	HBr		70	
12	1b	$(CH_3)_2CHMgCl$	HCl	77		
13	1c	$(CH_3)_3CMgCl$	HCl	56		
14	1d	$(CH_3)_3CMgCl$	HCl	56		
15	1d	$(CH_3)_2CHMgCl$	HCl	48		
16	1d	$CH_3CH_2CH_2MgCl$	HCl	75		
17	1d	$C_6H_5CH_2MgCl$	HCl	93		
18	1e	$(CH_3)_3CMgCl$	HCl	30		
19	1e	$(CH_3)_2CHMgCl$	HCl	92		
20	1f	$(CH_3)_2CHMgCl$	HCl	50		
21	1a	$(CH_3)_3CMgCl$	H_2SO_4		62	
22	1a	$CH_3CH_2CH_2MgBr$	H_2SO_4	89		
23	1a	$C_6H_5CH_2MgCl$	H_2SO_4	95		
24	1b	$(CH_3)_3CMgCl$	H_2SO_4			49
25	1b	$(CH_3)_2CHMgBr$	H_2SO_4			55
26	1b	$CH_3CH_2CH_2CHMgBr$	H_2SO_4			81
27	1c	CH_3MgI	H_2SO_4			44
28	1f	$C_6H_5CH_2MgCl$	H_2SO_4			53

* The CH_2Cl_2 extraction is nuetralized by $NaHCO_{3(aq)}$ solution.

when **2b**-**2f** are treated with ice cold 85% sulfuric acid (Scheme II). Hydroximoyl halides **3** are believed from α-nitroso halides **C** because the transient intense blue color always is observed when nitronates **2** are added to concentrated acids. α-Nitroso halides **C** arise if halide (from RMgX, MgX_2 and/or $HX_{(aq)}$) trap the protonated nitronates **A**, analogous to water in the Nef reaction, or the nitroso cation **B**. A similar reaction has been reported in which α-chloronitroso compounds are formed from nitronate salts using dry hydrogen chloride.[4] To the best of our knowledge, this is the first example of isolating hydroximoyl halides **3** and nitrile oxides **4** from the reactions of nitroalkenes with Grignard reagents.



Scheme II

It is known that nitrlle oxides **4** can undergo 1,3-dipolar cycloaddition with olefins or acetylenes to generate 2-isoxazoline or isoxazole respectively.[5] The reaction of pure nitrile oxides **4** or hydroximoyl halides **3** in the presence of triethylamine can react with diethyl fumarate, diethyl maleate or phenylacetylene to generate high yields (92-98%) of additional products. It is also easy to synthesize some intramolecular 1,3-dipolar cycloaddition products when β-nitrostyrenes[6] react with proper Grignard reagents (Scheme III).

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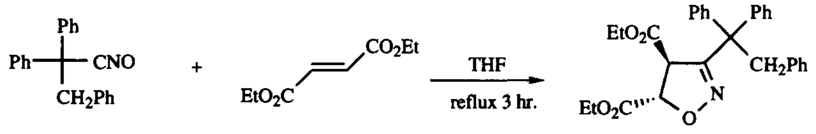
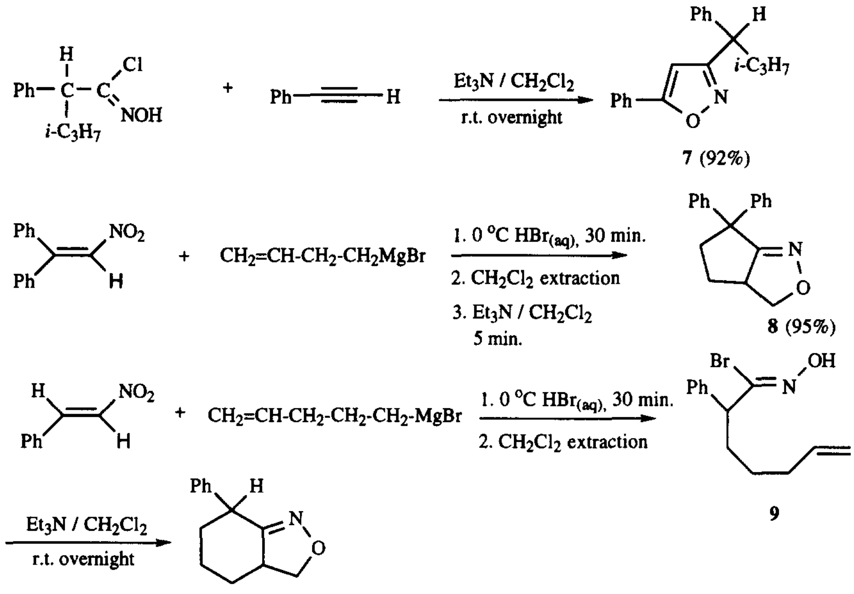


6 (98%)



Scheme III

References and Notes

1. (a) Kohler, E. P.; Stone, J. F. *J. Am. Chem. Soc.*, **1930**, 52, 761-768. (b) Buckley, G. D. *J. Chem. Soc.*,**1947**, 1494-1497. (c) Ashwood, M. S.; Bell, L. A.; Houghton, P. G.; Wright, S. H. B. *Synthesis*, **1988**, 379-381. (d) Barboni, L.; Bartoli, G.; Marcantoni, E.; Petrini, M.; Dalpozzo, R. *Chem. Soc. Perkin Trans I*. **1990**, 2133-2138.
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3. The general procedure is to add nitroalkene (2 mmol) in 10 mL THF to 10 mmol of the Grignard reagent in 30 mL of THF at -20 °C. Within 10 minutes, the solution is added to ice cold saturated aqueous HX (HCl 37%, HBr 48%, HI 57%) solution and stirred 30 minutes. The solution is extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated to give the products **3** or **4**. The CH_2Cl_2 extraction can be neutralized by $NaHCO_{3(aq)}$ or Et_3N to generate nitrile oxides **4** (entry 9) or furoxan (entry 15) after flash column separation in the absence of dipolarophile. The yields are based on NMR by using toluene or diiodomethane as internal standard.
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5. (a) Wade, P. A.; Amin, N. V.; Yen, H.-K.; Price, D. T.; Huhn, G. F. *J. Org. Chem.* **1984**, 49, 4595-4601. (b) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronate in Organic Synthesis* 1988, VCH, New York.
6. Compound **8**: MP 87 °C; ^{1}H-NMR(200MHz, $CDCl_3$) δ 7.40-7.12(m, 10H), 4.69-4.53(m, 1H), 4.00-3.78(m, 2H), 3.11-2.88(m, 2H), 2.18-2.01(m, 1H), 1.85-1.67(m, 1H); ^{13}C-NMR(200MHz, $CDCl_3$) δ 174.63, 144.23, 143.66, 128.86, 128.27, 127.61, 126.26, 127.03, 126.64, 75.45, 53.89, 53.67,43.95, 25.27. Calculated for $C_{18}H_{17}NO$: C, 82.10 ; H, 6.51 ; N, 5.32. Found: C, 81.99 ; H, 6.56 ; N, 5.11.

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