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Friedel–Crafts reaction of electron-rich (het)arenes with nitroalkenes

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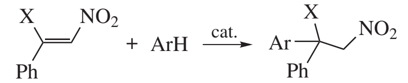
The Friedel–Crafts reaction between electron-rich (het)arenes and β-nitrostyrenes under MgI_2 or $Ca(NTf_2)_2$ catalysis affords 1-(het)aryl-2-nitro-1-phenylethanes in yields up to 94%.



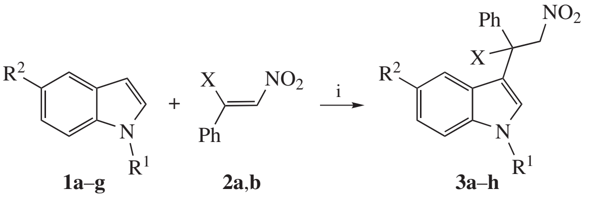
X = H or CO_2Et
cat. = MgI_2 or $Ca(NTf_2)_2$

15 examples
up to 94%

The Friedel–Crafts alkylation is one of the important reactions for C–C bond formation in organic chemistry. The use of nitroalkenes as electrophiles in this reaction has attracted significant interest in recent years. In fact, this process can be equally regarded as the Friedel–Crafts alkylation of the aromatic compound and the Michael addition at the double bond of nitroalkene. The activating effect of NO_2 group, as well as the ease of its transformation into other functional groups, makes these compounds promising building blocks for the synthesis of various pharmaceutical compounds.[1] Generally, the Friedel–Crafts addition to nitroalkenes is restricted to the reactions with indoles[2–21] and pyrroles,[22–26] however cases with other electron-enriched arenes are also documented.[27–32] When strongly electron deficient β-fluoro-β-nitrostyrenes were applied, the addition proceeded without catalyst.[33]

In our previous works, we investigated the addition of indole **1a** to activated olefins[34] (including the asymmetric version[35]) and to ethyl glyoxalate.[36] We found out that the reaction conditions (10% MgI_2 in CH_2Cl_2) were suitable for a wide range of Friedel–Crafts addition reactions characterized by high yields of the products and short reaction time. In the present work, we studied the addition of various electron-rich (het)arenes to *trans*-β-nitrostyrene **2a** and ethyl (*Z*)-3-nitro-2-phenylacrylate **2b**.

In the first experiments on the addition of indole to nitroalkenes, calcium salts were tested as the catalysts (Scheme 1), since in our previous studies they provided good yields in relative processes. Surprisingly, we discovered that MgI_2/CH_2Cl_2 system turned more suitable for Friedel–Crafts addition of indole to *trans*-β-nitrostyrene **2a**. In the case of ethyl (*Z*)-3-nitro-2-phenylacrylate **2b**, MgI_2 was completely inactive and the reaction did not proceed at all (see Scheme 1), whereas the use of $Ca(NTf_2)_2$ as the catalyst provided 90% yield of product **3h**. The reactions can be easily scaled up to a gram quantity: for 1 g scale of indole, the yields of adducts **3a** and **3h** were 90 and 88%, respectively.



1a–g **2a**,**b** **3a–h**

1a $R^1 = R^2 = H$
1b $R^1 = Me, R^2 = H$
1c $R^1 = H, R^2 = F$
1d $R^1 = H, R^2 = Cl$
1e $R^1 = H, R^2 = Br$
1f $R^1 = H, R^2 = Me$
1g $R^1 = H, R^2 = OMe$

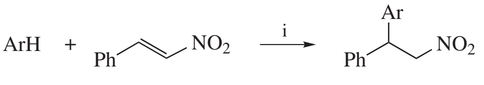
2a X = H
2b $X = CO_2Et$

Reactants	Product	Yield (%)
1a + **2a**	**3a**	93 (90)
1b + **2a**	**3b**	83
1c + **2a**	**3c**	90
1d + **2a**	**3d**	74
1e + **2a**	**3e**	94
1f + **2a**	**3f**	91
1g + **2a**	**3g**	78
1a + **2b**	**3h**	0 (90)

Scheme 1 *Reagents and conditions*: i, **1a–g** (0.5 mmol), **2a**,**b** (0.25 mmol), MgI_2 (0.025 mmol), CH_2Cl_2 (0.5 ml), 20 °C, 24 h. Yields given in parentheses relate to the use of $Ca(NTf_2)_2$ as the catalyst in $CHCl_3$ solution.

Next we investigated the effect of substituents in the indole molecule on the yield of the addition product. *N*-Methylindole formed an adduct **3b** in a slightly lower yield (83%). The introduction of fluorine or bromine atom at 5-position of indole almost did not change the yield of the reaction products **3c**,**e**, but in the case of 5-chloroindole **1d** the yield of **3d** decreased to 74%. 5-Methylindole **1f** afforded the corresponding product **3f** in 91% yield. The introduction of the electron donor methoxy group resulted in a lower yield (78%, product **3g**). In the case of 4-methoxyindole, the reaction gave a complex mixture in which the Friedel–Crafts addition product could not be identified. 5-Nitro- and 6-carboxymethylindoles almost did not react under indicated conditions due to their low reactivity, and after 48 h only traces of corresponding addition products were detected.

Further we studied various electron-enriched aromatic compounds in this reaction. Benzenes with MeO and Et_2N substituents participated in the reactions with **2a** in the presence of MgI_2. 1,3-Dimethoxybenzene **4** provided 68% yield of product **4a** (Scheme 2), 1,3,5-trimethoxybenzene gave a slightly lower yield (56%) of **4b**, while in *N*,*N*-diethylaniline the *para*-hydrogen atom was selectively substituted giving 62% yield of compound **4c**. As far as we know, this is the first example of the Lewis-acid catalyzed addition of electron-rich benzenes to *trans*-β-nitrostyrene. 2-Methylfuran also reacted with alkene **2**, however the yield of compound **4d** was only 44% due to the formation of various condensation products (see Scheme 2).

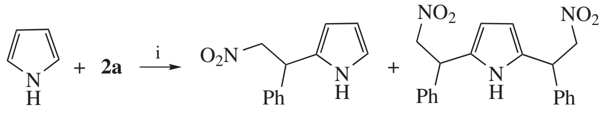


2a

4a Ar = $2,4\text{-}(MeO)_2C_6H_3$ (68%)
4b Ar = $2,4,6\text{-}(MeO)_3C_6H_2$ (56%)
4c Ar = $4\text{-}Et_2NC_6H_4$ (62%)
4d Ar = 5-methylfuran-2-yl (44%)

Scheme 2 *Reagents and conditions*: i, (het)arene (0.5 mmol), **2a** (0.25 mmol), MgI_2 (0.025 mmol), CH_2Cl_2 (0.5 ml), 20 °C, 24 h.

Pyrrole reacted with *trans*-β-nitrostyrene to form mono- and dialkylation products regardless of the *trans*-β-nitrostyrene–pyrrole ratio, therefore, excess of pyrrole was used to maximize the conversion of the *trans*-β-nitrostyrene (Scheme 3). Product **5** was successfully chromatographically separated from the mixture of isomeric disubstuituted pyrroles *dl*-**6** and *meso*-**6**, their yields being 43 and 31%, respectively. In the case of *N*-methylpyrrole, a mixture of mono- and dialkylation products was also formed, however this mixture could not be separated by column chromatography.

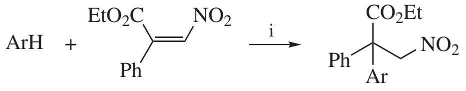


5
43%

dl-**6** + *meso*-**6**
Σ 31%

Scheme 3 *Reagents and conditions*: i, pyrrole (0.5 mmol), **2a** (0.25 mmol), MgI_2 (0.025 mmol), CH_2Cl_2 (0.5 ml), 20 °C, 24 h.

We also found that another electron deficient alkene, ethyl (*Z*)-3-nitro-2-phenylacrylate **2b**, did not react with 1,3-dimethoxybenzene, 1,3,5-trimethoxybenzene or 2-methylfuran even within 48 h. However, with $Ca(NTf_2)_2$ as the catalyst, *N*,*N*-diethylaniline formed the addition product **7a** in 37% yield in 48 h (Scheme 4). The addition products of pyrrole and *N*-methylpyrrole **7b** and **7c** were obtained in 81 and 66% yields, respectively. Polyalkylation products were not detected even in trace amounts. This is the first example of the addition of the aromatic compounds other than indole to ethyl (*Z*)-3-nitro-2-phenylacrylate.



2b

3h Ar = indol-3-yl (90%)
7a Ar = 4-$Et_2NC_6H_4$ (37%)
7b Ar = pyrrol-2-yl (81%)
7c Ar = 1-methylpyrrol-2-yl (66%)

Scheme 4 *Reagents and conditions*: i, (het)arene (0.5 mmol), **2b** (0.25 mmol), $Ca(NTf_2)_2$ (0.025 mmol), $CHCl_3$ (0.5 ml), 20 °C, 24 h.

In conclusion, the Friedel–Crafts reaction of electron-rich (het)arenes with *trans*-β-nitrostyrene and ethyl (*Z*)-3-nitro-2-phenylacrylate was studied. The MgI_2-catalyzed addition of substituted indoles to *trans*-β-nitrostyrene has been developed, this process affords high yields of the target products (up to 94%). For the first time, Lewis acid-catalyzed Friedel–Crafts addition of benzenes with electron donor substituents was accomplished in the presence of MgI_2 for *trans*-β-nitrostyrene and in the presence of $Ca(NTf_2)_2$ for ethyl (*Z*)-3-nitro-2-phenylacrylate. This procedure can be extended to the derivatives of 5-membered heterocycles, which can be synthesized in 44–81% yields. The method is very simple as all reactions were performed at room temperature under ambient atmosphere, solvents were used as purchased without special purification.

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Online Supplementary Materials

Supplementary data associated with this article (experimental details, ^1H and ^{13}C NMR spectra of compounds) can be found in the online version at doi: 10.1016/j.mencom.2019.03.005.

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