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Aza-Henry reaction of substituted nitroalkanes using α-formamidoaryl sulfones as *N*-acylimino equivalents

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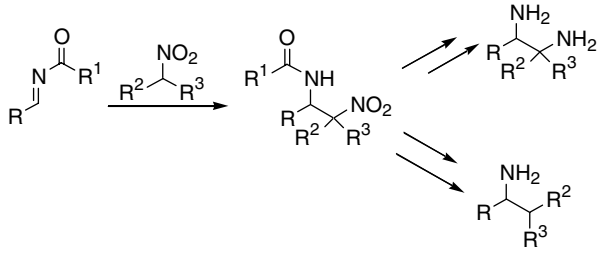
Abstract—Base-promoted elimination of *p*-toluenesulfinic acid from *N*-formamidoaryl sulfones leads to the corresponding *N*-acylimines that react with primary and secondary nitronate anions giving *anti*-β-formamido nitroderivatives in good yields and high diastereoselectivity.

The widespread interest in the nucleophilic addition of nitronate anions to azomethine compounds stems from the particularly high practical value of the obtained products bearing two nitrogen atoms with different oxidation status in adjacent position. Further synthetic manipulation of these derivatives provides a gathering of useful compounds, such as 1,2-diamines[1] and α-amino carbonyls prepared by reduction or Nef reaction of the nitro group (Scheme 1).[2]

A less exploited option consists in the replacement of the nitro function by hydrogen, leading to the corresponding monoamino derivative.[3] Concerning the nature of the imino derivative, *N*-arylimines react with lithium or silyl nitronates at low temperature giving predominantly *anti*-β-nitro amines, but activation of the imine by Lewis or Brønsted acids seems mandatory for an efficient addition.[4] The electrophilic aptitude of the azomethine carbon can be suitably enhanced by linking electron-withdrawing substituents at the nitrogen atom. In this context, *N*-acylimines are undoubtedly very electrophilic compounds that can be made to react with a large variety of nucleophilic reagents.[5] Direct synthesis of *N*-acylimines by condensation of their carbonyl and amide precursors does not represent a viable protocol. Conversely, base-promoted elimination of benzenesulfinic acid from α-amido sulfones usually provides the corresponding *N*-acylimines that must be immediately used in order to avoid extensive decomposition.[6] α-Amido sulfones are stable and mostly solid compounds that can be readily obtained by a three-component coupling of an aldehyde, amide and sodium benzenesulfinate.[7] The enhanced reactivity of *N*-carbamoylarylimines makes them ideal substrates for catalytic enantioselective aza-Henry reactions that are usually carried out at low temperature for prolonged reaction times (24–60 h), and require a large excess of nitroalkane (5–10 equiv).[8] A more profitable way to use α-amido sulfones consists in the in situ generation of the corresponding *N*-acylimine by a suitable base and its immediate reaction with a nitronate anion.[9] The nature of the acyl moiety has a deep impact on the reactivity of the *N*-acylimine and affects the reaction time as well as the efficiency of the related process. For practical reasons, carbamoyl groups are often preferred with respect to other acyl substituents in *N*-acylimines because these derivatives are more easily cleaved to the corresponding free amino groups.[10] However, for some purposes, *N*-formylamido sulfones have been demonstrated to be more effective than the corresponding *N*-carbamoyl derivatives.[11] A marked reactivity of *N*-acylimino derivatives would result in a shortening of reaction times and is particularly



Scheme 1.

Keywords: *N*-Acylimines; Aza-Henry reaction; 1,2-Diamines; Nitroalkanes; Sulfones.
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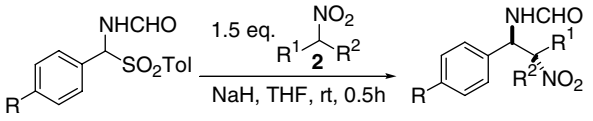
profitable when sterically hindered tertiary nitroalkanes are used as reagents. We have observed that *N*-formylaryl sulfones **1**[12] are able to react with different nitroalkanes **2** in the presence of sodium hydride, giving the corresponding β-formamido derivatives **3** in good yield (Scheme 2, Table 1).

After 45 min at room temperature, the addition of nitroalkanes **2** to the intermediate *N*-formylimine, produced by the elimination of *p*-toluenesulfinic acid from sulfones **1**, is complete and requires only a modest excess (1.5 equiv) of the nitro compound.[13] Nitromethane **2a** and primary nitroalkanes **2b**–**g** afford the corresponding *N*-formylamido nitro derivatives **3** in good yield (Table 1, entries 1–9). Compounds **3b**–**i** are obtained as an unseparable mixture of diastereomers in which *anti*-**3** strongly predominates. The enhanced reactivity of sulfones **1** is also demonstrated by their reaction with secondary nitroalkanes **2h**–**j** that allows the formation of adducts **3j**–**m** with the same efficiency observed for primary nitroalkanes (Table 1, entries 10–13). The relative stereochemistry of compounds **3** has been evaluated by transformation of nitro derivative **3b** into 1,2-diamine **4** (Scheme 3). Reduction of **3b** using SmI_2 affords the corresponding *N*-formyl amino derivative, which upon hydrolysis of the amido group in acid conditions leads to known *anti*-1,2-diamine **4**.[14]

Removal of the nitro group under reductive conditions, also referred as denitration, represents a profitable procedure that, when coupled with Henry reactions, ultimately allows the addition of an alkyl framework to C=X systems. Thus in this two-step process, nitronate anions act as equivalents of alkyl anions that are usually introduced by means of unstable organometallic reagents. Although a certain number of synthetic methods are available in the literature to realize this conversion,[3] the radical mediated substitution of the nitro group using Bu_3SnH as hydrogen atom donor is certainly far superior and general with respect to other related procedures.[15] This denitrating system is particularly effective when tertiary, benzylic or α-keto nitro derivatives are used as substrates because of the high stability of the corresponding alkyl radical that is formed as an intermediate. The effectiveness of this method has been



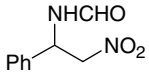
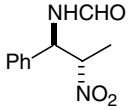
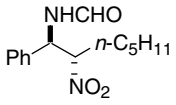
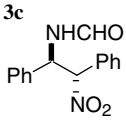
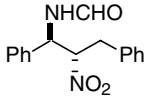
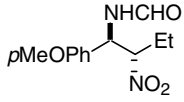
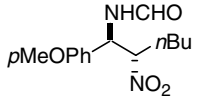
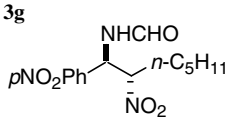
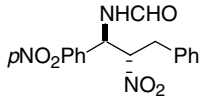
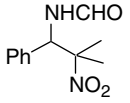
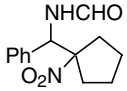
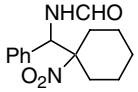
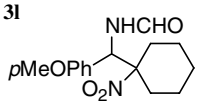
3

1a R = H
1b R = MeO
1c R = NO_2

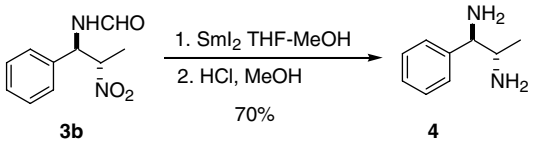
2a R^1= H; R^2= H
2b R^1= Me; R^2= H
2c R^1= Et; R^2= H
2d R^1= *n*-C_4H_9; R^2= H
2e R^1= *n*-C_5H_{11}; R^2= H
2f R^1= Ph; R^2= H
2g R^1= $PhCH_2$; R^2= H
2h R^1= Me; R^2= Me
2i R^1= R^2= $(CH_2)_4$
2j R^1= R^2= $(CH_2)_5$

Scheme 2.

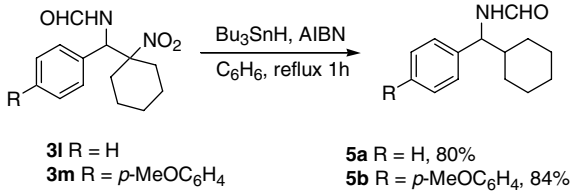
Table 1. Synthesis of *N*-Formyl-β-nitro derivatives **3** by reaction of *N*-formylaryl sulfones **1** with nitroalkanes **2**[a]

Entry	Sulfone	Nitroalkane	Products[b]	Yield (%)[c] (dr)
1	**1a**	**2a**	 **3a**	90
2	**1a**	**2b**	 **3b**	91 (90:10)
3	**1a**	**2e**	 **3c**	90 (90:10)
4	**1a**	**2f**	 **3d**	95 (95:5)
5	**1a**	**2g**	 **3e**	90 (95:5)
6	**1b**	**2c**	 **3f**	94 (90:10)
7	**1b**	**2d**	 **3g**	93 (92:8)
8	**1c**	**2e**	 **3h**	88 (90:10)
9	**1c**	**2g**	 **3i**	89 (95:5)
10	**1a**	**2h**	 **3j**	91
11	**1a**	**2i**	 **3k**	87
12	**1a**	**2j**	 **3l**	83
13	**1b**	**2j**	 **3m**	80

[a] All reactions were carried out at rt in THF, in the presence of NaH.
[b] All products were identified on the basis of their IR and NMR spectra.
[c] Yields of pure products isolated by column chromatography.



Scheme 3.



Scheme 4.

checked on a couple of tertiary *N*-formylamido nitro derivatives **3l**,**m**, which upon heating in a benzene solution in the presence of 2 equiv of Bu_3SnH and a catalytic amount of a radical initiator (AIBN) give the corresponding formylamides **5** in good yield (Scheme 4).

In conclusion, *N*-formylaryl sulfones **1** promptly react with nitroalkanes **2** in the presence of NaH giving the corresponding aza-Henry adducts **3** in good yield and high *anti*-diastereoselectivity. Reduction of the nitro group and hydrolysis of the formyl protection from *N*-formylamido nitro derivatives **3** provide an entry to 1,2-diamino derivatives. Products **3** obtained by reaction of secondary nitroalkanes are particularly prone to radical induced reduction that allows the preparation of denitrated product **5**.

Acknowledgements

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13. General procedure for aza-Henry reaction on *N*-formylaryl sulfones **1**: To a stirred suspension of NaH (3.0 mmol) in dry THF (15 mL) the appropriate nitroalkane **2** (1.5 mmol) was added at room temperature. After stirring for 30 min, sulfone **1** (1.0 mmol) dissolved in dry THF (5 ml) was added dropwise and the white suspension was stirred for 45 min at room temperature. The reaction mixture was then quenched with satd NH_4Cl (5 mL), extracted with CH_2Cl_2 (3×10 mL) and the organic phase dried over $MgSO_4$. After removal of the solvent at reduced pressure, the crude nitro derivative obtained was purified by column chromatography ($CHCl_3$/MeOH 98:2). Selected data of compounds—**3d**: mp 89–90 °C (ethyl acetate–hexane). IR (cm^{-1}, KBr): 3290;1680:1550. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.99 (t, 3H, $J = 7.3$ Hz); 1.69–2.15 (m, 2H); 3.78 (s, 3H); 4.66–4.84 (m, 1H); 5.41–5.60 (m, 1H); 6.54 (d, 1H, $J = 9.5$ Hz); 6.91 (d, 2H, $J = 8.8$ Hz); 7.24 (d, 2H, $J = 8.8$ Hz); 8.25 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.5, 23.9, 55.5, 58.5, 92.7, 114.8, 127.5, 128.7, 160.7, 164.1. Compound **3l**: Oil. IR (cm^{-1}, neat): 3310, 1688, 1555. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.10–1.45 (m, 2H); 1.55–1.95 (m, 4H); 2.18–2.24 (m, 2H); 2.40–2.55 (m, 1H); 2.60–2.80 (m, 1H); 5.40 (d, 1H, $J = 10.2$ Hz); 6.43 (d, 1H, $J = 10.2$ Hz), 7.15–7.45 (m, 5H); 8.20 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 22.1, 24.3, 31.0, 57.0, 99.5, 127.6, 128.2, 131.5, 160.7, 162.9.
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