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Arylation of nitromethane: masked nucleophilic formylation of fluoroquinolones

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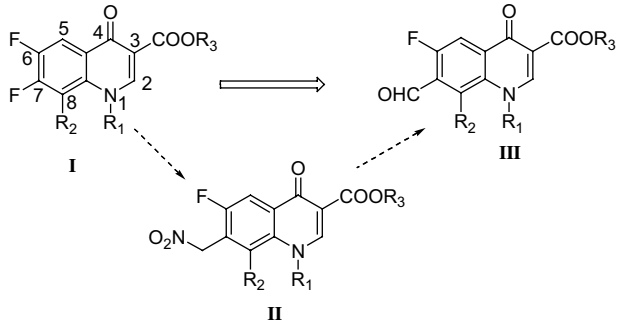
Abstract—Arylation of nitromethane with fluoroquinolones have been achieved through an S_NAr reaction under mild conditions in excellent yield. Subsequently the nitromethyl derivatives obtained were readily transformed into the corresponding aryl aldehyde, overall as an equivalent process of nucleophilic formylation.

In our continuous pursuit of new antibacterial fluoroquinolones, the formylation at C-7 of the fluoroquinolones intermediate (**I**, Scheme 1) would expedite the synthesis of a series of newly designed derivatives.[1] However, given the electron-deficient nature of this aromatic nucleus, standard formylation methods are not plausible.[2] Bearing in mind that Nef reaction is a well-known 'umpolung' method for the formation of a carbonyl,[3] arylastion of nitromethane by these aromatic nuclei followed by Nef reaction would be a straightforward pathway to achieve this transformation (Scheme 1).



Scheme 1.

While Henry condensation and Michael addition of nitroalkane are widely employed in forming C–C bonds,[4] constructing such a bond between an arene and the α-carbon of a nitroalkane is challenging in organic synthesis. Few reports have been published concerning this transformation in the last several decades. The most recent protocol was developed by Buchwald based on the Pd-catalyzed arylation of nitroalkane.[5] This is the first general approach, but it did not work with nitromethane and obviously aryl halides are confined to those which are active in catalytic coupling reaction (mostly aryl bromide as reported). Additionally this procedure necessitates toxic reagents and particular substituted phosphine ligands, which themselves are laborious to synthesis. Prior to this report, most of the other studies were based on the nucleophilic aromatic substitution (S_NAR) reaction of nitroalkanyl anion (nitronate) with electro-deficient aromatic nuclei. Among all of the examples reported,[6–9] only aromatic compounds with (multi-) nitro groups were employed as the substrate, most likely in order to enhance the S_NAR reactivity of the aromatic ring, and all resulted in low yield. Here we report the successful arylation of nitromethane through an S_NAR reaction with fluoroquinolones. The resulting nitromethyl derivatives can be transformed into the corresponding arylaldehyde, which is not straightforward to obtain by other methods. Thus the overall process can be considered as a nucleophilic formylation of a reactive arene, in which nitromethane serves as the synthon for formyl anion.

To our understanding the ambident and weak nucleophilicity of the nitronate anion in part accounts for the

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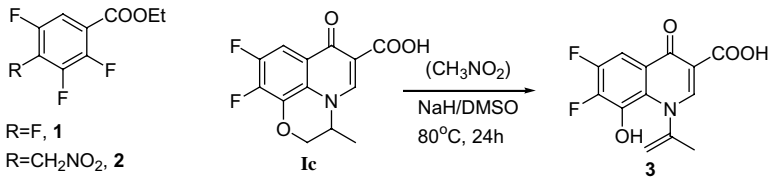


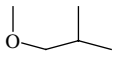
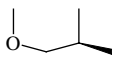
Scheme 2.

erratic nature of them in S_NAR reaction. Therefore in a preliminary study ethyl 2,3,4,5-tetrofluorobenzenecarboxylate (**1**, Scheme 2) was chosen as the model substrate because of its conceivable high reactivity in S_NAR reaction. Promisingly **1** reacted readily with nitromethane in the presence of NaH at room temperature. Although both C2 and C4 are potential reaction sites, product **2** was isolated in high yield. The structure of **2** was characterized through MS, ^1H NMR, and HMBC. From the spectroscopy of HMBC, among the six carbon atoms of the aromatic ring, the three bound to a fluorine could be discriminated easily from the other three because of their higher chemical shift value (145–158 as to 110–125). Among the other three, one of them coupled with both Ar–H and the proton of CH_2NO_2, another one coupled with only Ar–H, while the third one coupled with neither of those protons. The absence of two carbons coupling with both Ar–H and CH_2NO_2 suggests the structure **2** rather than the *ortho* nitromethyl counterpart. In the meantime all the other signals are in agreement with this structure **2** as well. Regarding the ambident nature of the nitromethyl anion, the S_NAr reaction took place on the carbon atom exclusively; O-substitution, often occurred in other reports,[6,8] was not observed in this case. The S_NAr reactions of fluoroquinolones with nitromethane were studied further. The results are summarized in Table 1.

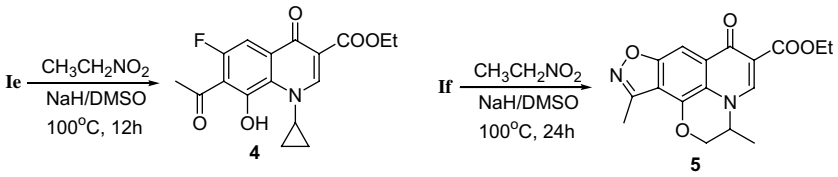
The well-investigated S_NAr reaction of fluoroquinolones with amines suggests quinoline-3-carboxylic acids (Scheme 1, **I**, $R_3 = H$) are more active than the corresponding alkyl esters (**I**, R_3 = alkyl) in S_NAr reaction with amines and thus preferable in the displacement of the 7-halogen by incoming amines.[10] This reactivity difference is attributed to the intra-molecular hydrogen bond between the 4-carbonyl and 3-COOH, which enhance the electro-withdrawing capability of the carbonyl and consequently the activity of the 7-halogen. Considering these observations, **Ia** (Scheme 1 and Table 1) was chosen first as the substrate and as expected, the reaction of **Ia** with nitromethane in the presence of NaH afford **IIa** in good yield. This nitromethylation proceeded well with **Ib** but surprisingly substrate **Ic** (Scheme 2) underwent elimination under the same condition and compound **3** was isolated as the main product in good yield. Because the elimination of HF from the 1-(2-fluoroethyl) substituent of some quinolones (**I**, $R_1 = CH_2CH_2F$) into an ethylenyl under basic condition was observed previously in other studies,[10] the formation of **3** was believed to be the resulting product due to a similar transformation. Actually, identical product was also obtained from a comparison experiment stirring the mixture of **Ic** and NaH without the presence of nitromethane.

Interestingly the S_NAR reaction of **Id–g**, esters of carboxylic acids **Ia–c**, with nitromethane proceeded more readily than the acids themselves. Fluorine of ester **Id** and **Ie** could be displaced by nitromethyl anion at room temperature while that of acid **Ia** and **Ib** only proceeded at elevated temperature. Excellent yields were obtained with esters after simple workup. The product **IId–g** can be used directly for the next step without any further purification. Moreover, it is noteworthy that substrate **If**, the corresponding ester of the acid **Ic**, could be nitromethylated satisfactorily. It seems for substrate **Ic**

Table 1. S_NAR reaction of fluoroquinolones with nitromethane (**I** → **II**)

Entry	Substrate				Conditions		Product[a]			
	No.	R_2	R_1	R_3	Time (h)/ T (°C)	Base	No.	Mp (°C)	Yield (%)	δ CH_2NO_2[b] (ppm)
1	**Ia**	F	Et	H	4/80	NaH	**IIa**	244–246	72	6.17 (s)
2	**Ib**	F	Cp[c]	H	4/80	NaH	**IIb**	265–267	74	5.76 (s)
3	**Id**	F	Et	Et	2/rt	NaH	**IId**	172–174	82	6.17 (s)
4	**Ie**	F	Cp	Et	3/rt	NaH	**IIe**	188–189	93	6.11 (s)
5	**Ie**	F	Cp	Et	3/50	DBU	**IIe**	188–189	90	
6	**Ie**	F	Cp	Et	6/60	K_2CO_3	**IIe**	188–189	89	
7	**If**			Et	4/50	NaH	**IIf**	214–216	91	5.89 (q, J = 16.8)
8	**Ig**			Et	4/50	NaH	**IIg**	204–206	89	5.90 (d, 1H, J = 15.6), 5.96 (d, 1H, J = 15.6)

[a] All products were isolated and characterized by HRMS, ^1H NMR, and CHN analyses.
[b] ^1H NMR chemical shift in $CDCl_3$ relative to TMS except **If** in DMSO-d_6.
[c] Cp = cyclopropanyl.



Scheme 3.

the S_NAr reaction with nitromethane was so sluggish that the elimination of **Ic** prevailed under strong basic condition. One factor which may account for these results might be the difference in the nucleophilic species. Under the reaction conditions nitromethyl anion is formed to act as a nucleophilic 'attacker', the quinoline-3-carboxylic acid is also in its salt form, so it might be hard for nitromethyl anion to reach this salt rather than the corresponding ester. On the other hand when amine serves as the nucleophilic species, access to both quinolinecarboxylic acid and ester could not be a decisive factor.

Further the experiment indicated that weaker bases promoted this reaction as effective as strong base when esters were chosen as substrates. For instance DBU worked as efficiently as NaH and did not form DBU adduct with arylfluoride as reported previously.[8] Inorganic base such as K_2CO_3 could be employed as well, in both cases **IIe** was cleanly furnished without substantial loss of yield. In comparison, Suzuki observed the delicate role the base played in nitromethylation of dinitroarene.[9]

However, the adaptability of this approach to nitroethane was not so satisfactory. In our experiment the condition had to be harsher than that of nitromethane to drive this reaction, which suggests lower reactivity of this more stereo-hindered nitronate anion, and thus resulted in a more complicated mixture of products. The reaction of **Ie** with nitroethane afforded **4** as the main product; presumably the initial S_NAR reaction product underwent further S_NAR process and/or rearrangement. Starting with **If** and nitroethane, **5** was isolated along with other unidentified products. Previously Suzuki and co-workers also identified some oxime in reaction of nitroethane with dinitroarene, it is likely that in our case intramolecular S_NAR took place after the formation of the oxime (Scheme 3).

Comparing with the examples reported previously, these results suggest electron-deficient arylhalide other than aromatic nitro compound could achieve good results in S_NAr reaction with nitroalkane. Nitro aromatic species are more likely to introduce vicarious nucleophilic substitution or single electron transfer (SET) reaction, which could complicate the pathway and then lead to a multitude of products in most case.

The transformation of primary or secondary nitroparaffin into the corresponding aldehyde or ketone has been known as Nef reaction.[3] Several attempts following the reported classic[11] or reductive[12] Nef reaction procedure failed to convert the nitromethylated derivatives **IIe** into the corresponding aldehyde **IIIe**, presumably because of the insolubility of **IIe** and/or its nitronate anion in the aqueous reaction medium. When methanol was chosen as the solvent the solubility of the nitronate anion was improved, and the aldehyde **IIIe** was obtained through oxidative Nef reaction with $KMnO_4$.[13] Under this condition nitromethyl derivatives **IId–g** were smoothly transformed into corresponding aldehyde **IIId–g**.[14,15] All the results were included in Table 2.

Table 2. Preparation of aldehyde **IIId–g** (**I** → **III**)

Substrate	Product	Yield[a] (%)	Mp (°C)	δ CHO[b] (ppm)
Id	**IIId**	64	168–170	10.41
Ie	**IIIe**	68	184–186	10.41
If	**IIIf**	64	179–182	10.49
Ig	**IIIg**	66	187–189	10.50

[a] After crystallization from acetone.
[b] ^1H NMR chemical shift in $CDCl_3$ relative to TMS.

In conclusion, we have found that arylation of nitromethane with fluoroquinolones can be achieved under mild condition in excellent yield. Our results suggest certain arylhalide are better substrate than nitro aromatic compounds in S_NAR with nitroalkane. Followed by Nef reaction, the original arylhalide has been readily transformed into the corresponding aryl aldehyde, overall as an equivalent process of nucleophilic formylation.

Acknowledgments

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14. General procedure for the preparation of **II**: Nitromethane (15 mmol) in DMSO (5 mL) was dropped into the suspension of NaH (15 mmol) in 15 mL of dry DMSO with stirring. After the bubbling subsided, **I** (5 mmol) was added; the mixture was stirred (temperature and duration time as indicated in Table 1) and then poured into ice-water; acidified with 6 N HCl, then extracted with ethyl acetate. The organic extraction was washed with water and brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent in vacuum gave a residue, which was recrystallized from alcohol to afford **II**.
15. General procedure of the preparation of **III**: A stirred suspension of **II** (20 mmol) in methanol (140 mL) was cooled to −10 to 5 °C and then a freshly prepared solution of KOH (60 mmol) in methanol (200 mL) was added dropwise. After stirring for an additional 30 min, a solution of $KMnO_4$ (2.2 g, 13.4 mmol) and MgSO4 (60 mmol) in water (600 mL) was added dropwise with vigorous stirring. When the reaction was complete, the mixture was filtered over a thin layer of Celite. The filtrate was extracted with CH_2Cl_2 and the extract was washed with saturated Na_2CO_3, water, and brine successively and then dried over $MgSO_4$. Removal of the solvent in vacuum gave a residue that was recrystallized from acetone to afford **III**.