JOC Article

Selective Ortho Methylation of Nitroheteroaryls by Vicarious Nucleophilic Substitution

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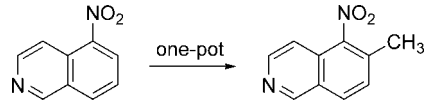

An efficient and scalable three-step one-pot approach to 6-methyl-5-nitroisoquinoline (**1**) from inexpensive 5-nitroisoquinoline, utilizing the vicarious nucleophilic substitution (VNS) as a key step, is described. The optimized reaction conditions can be applied to a limited number of other aromatic and heteroaromatic nitro compounds. Attempts to understand the observed selectivity in the VNS step led to the discovery of two new reaction pathways under VNS conditions, one leading to an isoxazole and the other resulting in the formal cyclopropanation of an aromatic nitro compound.

Introduction

In support of research programs we were charged with providing quantities of 6-methyl-5-nitroisoquinoline (**1**). It is a versatile heterocyclic building block (Scheme 1). In particular, the *o*-methyl-substituted nitroarene motif present in this molecule is amenable to the Leimgruber−Batcho indole synthesis.[1,2] Alternatively, the nitro group can be reduced to an amine group, thereby allowing access to further functionalization (Buchwald−Hartwig-amination and other C−N-couplings, Sandmeyer and related reactions). Finally the isoquinoline can be transformed to the *N*-oxide, which then allows for direct and indirect nucleophilic substitution reactions at the 1-position.

Several traditional approaches to substituted isoquinolines exist in the literature.[3] The majority rely on a de novo construction of an isoquinoline ring system starting from an electron-rich aromatic aldehyde[3a,b,e,g] or amine.[3c] For example, 6-methylisoquinoline (**2**) was synthesized starting from *p*-tolualdehyde, using a modified Pomeranz−Fritsch reaction (Scheme 2).[3g] The ring-closing step, a common key transformation of all the published approaches, is in this case affected by a large excess of titanium tetrachloride, which leads to problematic workups upon scale-up. 6-Methylisoquinoline (**2**) undergoes a selective nitration affording 6-methyl-5-nitroisoquinoline (**1**).[2] This step is complicated by the need to neutralize large volumes of concentrated sulfuric acid on a kilogram scale. In our hands the overall sequence resulted in an overall yield of 50−55% for the synthesis of **1**. Both steps generate significant quantities of inorganic salts as waste, thereby making this approach unattractive from both an economic and environmental perspective. We were therefore interested in an alternative more efficient approach to **1**.

Results and Discussion

We were intrigued whether the desired compound **1** could be accessed by a conjugate addition of a methyl anion equivalent to the formal Michael acceptor 5-nitroisoquinoline (**3**) followed by oxidative rearomatization.[4,5] Unfortunately, the addition of methyllithium to nitroarene **3** proceeded in only modest regioselectivity (Scheme 3). The intermediates were readily oxidized in situ by addition of bromine followed by triethylamine,[6] to afford a mixture of regioisomeric products **1** and **4** (ortho/para

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(1) (a) Batcho, A. D.; Leimgruber, W. *Org. Synth.* **1985**, *63*, 214. (b) Clark, R. D.; Repke, D. B. *Heterocycles* **1984**, *22*, 195.

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(5) 5-Nitroisoquinoline (**3**) is readily available ($350/kg).
(6) Kienzle, F. *Helv. Chim. Acta* **1978**, *61*, 449.

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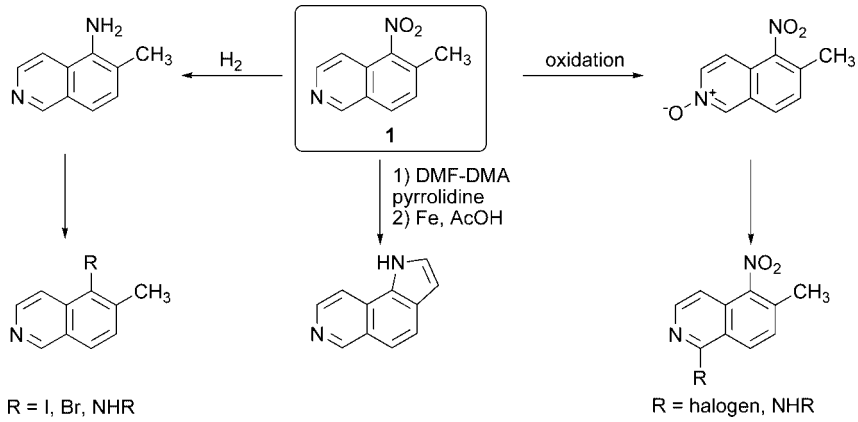
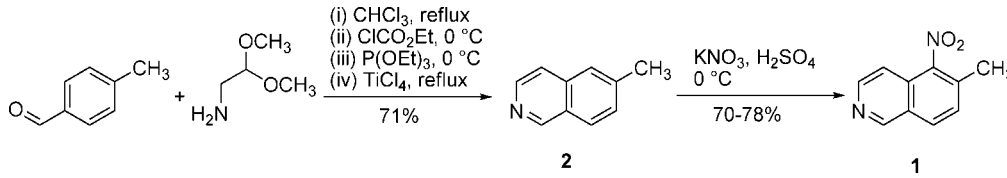
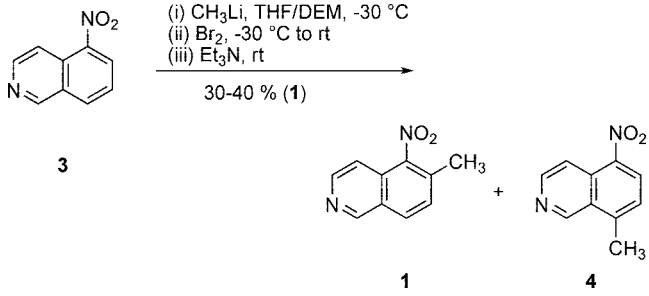
SCHEME 1. 6-Methyl-5-nitroisoquinoline as a Versatile Building Block



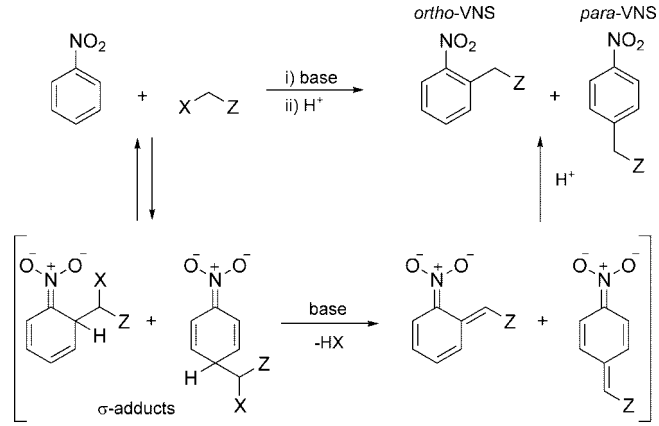
SCHEME 2. Original Synthesis of 1 Using the Pomeranz−Fritsch Reaction



SCHEME 3. Addition of Methyllithium to 5-Nitroisoquinoline



SCHEME 4. Vicarious Nucleophilic Substitution



X = leaving group (e.g. Cl, Br, OPh, SPh, etc.)
Z = carboanion stabilizing group (e.g. SO_2Ph, CN, CO_2Et, Cl, Ar, etc.)
base/solvent = KOH, NaOH, KO^{t}Bu / DMF, THF

ratio 2.5/1.0 as judged by ^{1}H NMR). Chromatographic separation afforded the required major ortho-isomer **1** in 30−40% yield.[7] The observed selectivity for this reaction is in agreement with literature reports on similar systems.[8] Although the methyllithium addition was not synthetically useful, the preference for a 1,4-addition versus 1,6-addition suggested that this approach could be viable with a suitable methyl anion equivalent.

The vicarious nucleophilic substitution of hydrogen (VNS) offers a convenient approach for the functionalization of aromatic and heteroaromatic nitro compounds (Scheme 4).[9,10] Reaction of a stabilized carbanion with an aromatic nitro compound leads to the formation of ortho- and para-substituted products. The reaction mechanism has been postulated to proceed via intermediate σ-adducts, that undergo 1,2-elimination to afford the substituted products.[11] The ortho/para ratio is highly dependent on the substrate, the nature of the nucleophile, and reaction conditions. Several weak acid nucleophiles, which could serve as a surrogate for a methyl anion under VNS conditions, were considered for the synthesis of **1**: chloroform,[12a] tribromomethane,[12a] trimethylsulfoxonium iodide,[12b] trimethylsulfonium iodide,[12c] and ethyl chloroacetate.[13] However, transforming the initial VNS product into **1** could pose problems in some of these cases. Interestingly, ethyl chloroacetate has been previously used for the synthesis of methylnitrobenzenes by using a three-step sequence: VNS, hydrolysis, and decarboxylation.[14] On the basis of this precedent we decided to start our investigations using the VNS conditions described in the literature.

Addition of a mixture of **3** and ethyl chloroacetate (1.1 equiv) into a solution of potassium *tert*-butoxide (2.2 equiv) in THF

(7) The minor para isomer **4** was not isolated.
(8) For addition of ethyl magnesium bromide to 4-nitroindole see: Quick, J.; Saha, B. *Tetrahedron Lett.* **1994**, *35*, 8553.
(9) Golinski, J.; Mąkosza, M. *Tetrahedron Lett.* **1978**, *19*, 3495.
(10) For general reviews see: (a) Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* **1987**, *20*, 282. (b) Mąkosza, M. *Synthesis* **1991**, 103.
(11) (a) Lemek, T.; Mąkosza, M.; Stephenson, D. S.; Mayr, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 2793. (b) Mąkosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* **2002**, *67*, 394.
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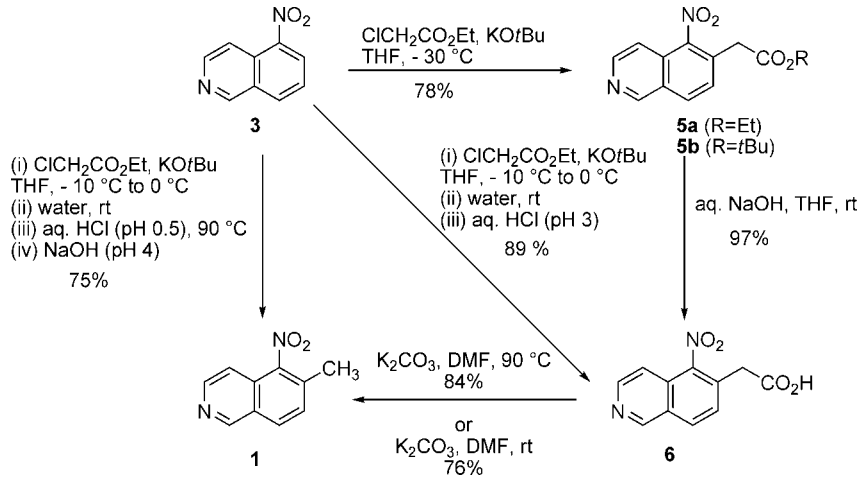
(13) (a) Mudryk, B.; Mąkosza, M. *Synthesis* **1988**, 1007.
(14) A sequential approach has been reported previously, but the authors specifically mention that a one-pot process failed for their product of interest (1,2,5-trichloro-3-methyl-4-nitro-benzene). See: Bull, D. J.; Fray, J.; Mackenny, M. C.; Malloy, K. A. *Synlett* **1996**, 647.

SCHEME 5. VNS Reactions with 5-Nitroisoquinoline



at −30 °C led to a rapid and regioselective addition−elimination via VNS pathway (Scheme 5). No para-isomer could be detected by ^{1}H NMR of the crude reaction mixture. The VNS product **5** could be isolated by crystallization after an aqueous workup in 78% yield. Mild saponification with aqueous sodium hydroxide, followed by acidification afforded the corresponding acid **6** in 97% yield. Traces of **1** were already present in the isolated acid suggesting a facile decarboxylation process with this substrate. Base-promoted decarboxylation of **6** afforded the desired 6-methyl-5-nitroisoquinoline (**1**) after a simple addition of water and filtration in 84% yield and excellent chemical purity (99.5% by HPLC) (64% overall yield from **3**). Hereby the VNS reaction had been established as a viable route for the synthesis of **1**, and subsequently we focused our efforts on improving the overall efficiency of the process.

Due to economic reasons it was desirable to perform the VNS under less cryogenic conditions. The reaction can be conducted at −10 to 0 °C without significant impact on the product quality. The formation of the transesterification product **5b** (R = *t*Bu) is observed at slightly elevated, but still relatively low levels (<5%) compared to reaction at −30 °C. This byproduct leads to the same acid **6** after the hydrolysis step. The saponification of **5** can be run as a through process by simple addition of water to the reaction mixture. The excess of base that is utilized in the VNS reaction is sufficient for complete hydrolysis of the ester at room temperature. The acid intermediate **6** is isolated by pH adjustment with HCl in good yield (89%) and purity (92% **6**, 6% **1**). The carboxylic acid can be decarboxylated under very mild conditions by using potassium carbonate in DMF at room temperature. The resulting product **1** is isolated in good yield and excellent purity (76%, 100% by HPLC).[15] All attempts to perform the decarboxylation under basic conditions as a one-pot process failed. The presence of water seemed to be detrimental to the decarboxylation—direct heating (80 °C) of the basic reaction medium (THF/water) after hydrolysis led to incomplete conversions even after prolonged time (16 h: 33% **1**, 66% **6**). The extraction of the crude acid into an organic solvent (2-methyltetrahydrofuran) followed by thermal decarboxylation at reflux gave complete conversion of **6** to **1**. However, the relatively low solubility of **6** in 2-methyltetrahydrofuran required a large solvent volume (60 mL/g), making this procedure inefficient. To circumvent the extraction of **6** the decarboxylation was investigated, under acidic conditions, to afford a three-step one-pot procedure for the synthesis of **1**. After conducting the VNS reaction under normal conditions in THF, water was added to allow the hydrolysis of the ethyl ester. After complete hydrolysis, residual amounts of starting material **3** and intermediate **5** were removed by washing with isopropyl acetate. The basic aqueous solution of **6** was adjusted to pH 0.5 with HCl and heated to 90 °C for 6 h, thereby affording complete decarboxylation. After adjustment of the reaction mixture to pH 4 with NaOH the product **1** was isolated by simple filtration in good overall yield (75%) and acceptable purity (97.6% by HPLC). The purity could be upgraded to >99.5% by recrystallization from DMF/water (92% recovery). This procedure allowed access to the 6-methyl-5-nitroisoquinoline (**1**) on a kilogram scale.

Prompted by the successful demonstration of a scalable ortho-methylation process we set out to evaluate the substrate scope of this methodology. Several aromatic and heteroaromatic nitro-compounds were chosen and subjected to one-pot and/or two-pot methylation conditions. The results are summarized in the Table 1.[16] 8-Nitroquinoline (**7**) performs well in the one-pot methylation process affording 62% yield of the desired product (**8**). Reaction with 6-nitroquinoline (**9**) proceeds uneventfully by application of the one-pot process leading to **10** in 74%. Gratifyingly only one of the two possible *o*-methyl-substituted products is formed exclusively. 5-Nitroquinoline (**11**) affords the product **12** in good yield (76%) with use of the two-pot procedure. However, decarboxylation of the intermediate acid as a one-pot process under strongly acidic conditions failed for this substrate. Application of the method to 1-nitronaphthalene (**13**) was also challenging. The one-pot process failed, leading to low conversion during the decarboxylation under acidic conditions, presumably due to lack of a basic functionality on the ring system. Application of the two-pot procedure led to a moderate yield of **14** (50%). Use of 3-nitropyridine (**15**) in the VNS process led to a relatively clean reaction profile in the initial addition, but the subsequent reaction steps gave dark-colored polymeric impurities. These byproducts presented difficulties in the reaction workup, only allowing isolation of product **16** in low yield (20%). Several other substrates were investigated but either incomplete conversion (2-phenylnitrobenzene) or unselective reaction profiles (2-methyl-8-nitroquinoline, 6-nitrobenzothiazole, 4-nitro-2,1,3-benzothiadiazole, 1-chloro-4-nitrobenzene, and 1-nitro-4-trifluoromethylbenzene) were observed in the initial VNS step. The limited substrate scope highlighted two key requirements for a successful application of this ortho-methylation reaction. A relatively clean reaction profile in the initial VNS step is necessary, since the crude

SCHEME 6. VNS Reactions with 5-Nitroisoquinoline

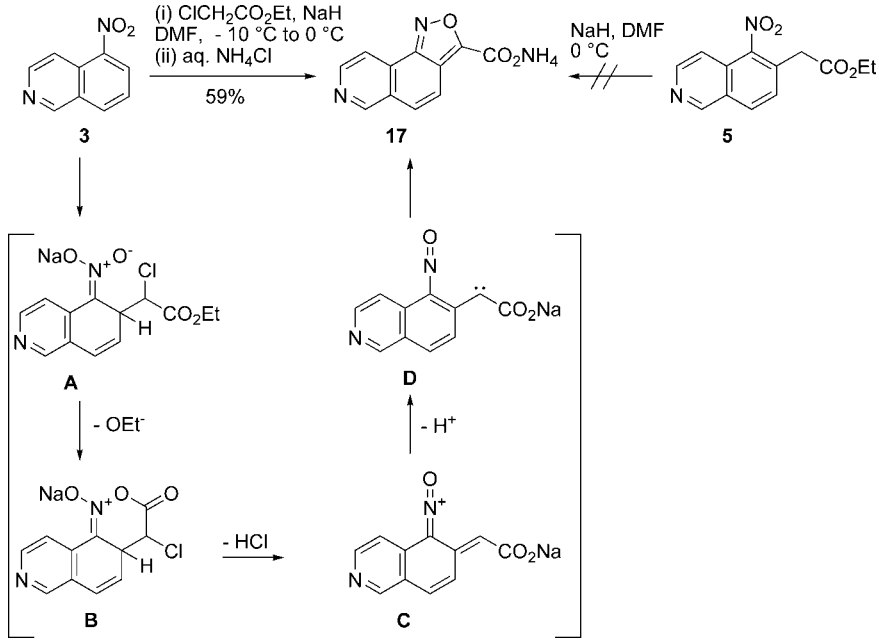


TABLE 1. Substrate Scope for Ortho Methylation

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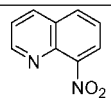
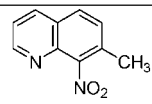
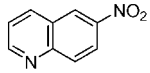
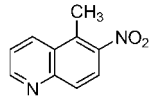
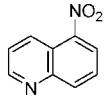
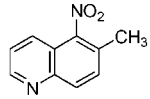
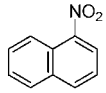
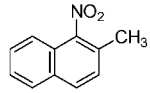
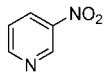
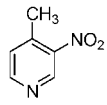
1	 7	 8	62[a]
2	 9	 10	74[a]
3	 11	 12	76[b]
4	 13	 14	50[b]
5	 15	 16	20[a]

[a] One-pot process (for detailed conditions see Supporting Information). [b] Two-pot process with isolation of intermediate acid (for detailed conditions see Supporting Information).

reaction mixture is carried forward without isolation at the VNS stage. The presence of a sufficiently basic nitrogen atom to allow protonation in the decarboxylation step under acidic conditions is a requirement for application of the one-pot process.

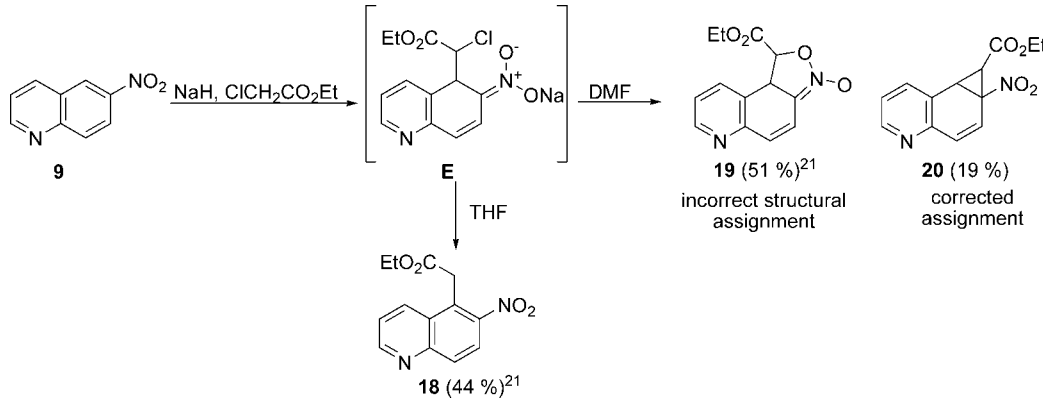
Having experienced some of the limitations of the methodology we were interested in gaining a deeper understanding for the observed chemo- and regioselectivity of the VNS reaction. Good ortho-selectivities have been previously reported with use of potassium *tert*-butoxide in THF. This had been rationalized by the presence of tight ion pairs in this solvent system, thereby allowing precoordination of the potassium enolate to the negatively charged oxygen atoms of the nitro-group and subsequent directed attack at the neighboring ortho-position.[17] The role of the cation in the reaction of 5-nitroisoquinoline with ethyl chloroacetate was evaluated. Attempted disruption of the precoordination by addition of an equimolar amount of 18-crown-6 led to inconclusive results. The reaction was sluggish due to decreased solubility and the ortho-substitututed product was observed as a major product. Replacement of potassium *tert*-butoxide by sodium *tert*-butoxide led to a similar reaction profile, suggesting that sodium is capable of an equivalent precoordination function. We next sought to explore sodium hydride as base in our system. Mąkosza had reported that reaction of ethyl chloroacetate with nitrobenzene in the presence of sodium hydride in DMSO afforded only trace amounts of VNS products.[18] In contrast, reaction of ethyl 2-chloropropionate with nitrobenzene in the presence of sodium hydride in DMF was reported to lead to exclusive formation of the para-substituted VNS product.[19] Addition of sodium hydride to a mixture of 5-nitroisoquinoline (**3**) and ethyl chloroacetate in DMF, followed by a buffered quench (aqueous ammonium chloride) led to formation of an unexpected new heterocycle in 59% yield (Scheme 6). The structure of this product was assigned as ammonium salt **17** by ^{1}H, ^{13}C NMR, and LC/MS. Use of an aqueous quench led to the isolation of the analogous sodium salt of **17**. Subjection of the previously isolated VNS product **5** to the same reaction conditions (NaH in DMF) led to no conversion to this new heterocycle, thereby suggesting an

(15) The yield for this step ranged from 76% to 84%, depending on the efficiency of the crystallization.

(16) The reaction temperature for the VNS step had to be optimized for some of the substrates. For optimized individual conditions refer to the Experimental Section.

(17) Mąkosza, M.; Glinka, T.; Kinowski, A. *Tetrahedron* **1984**, *40*, 1863.
(18) Mąkosza, M.; Winiarski, J. *J. Org. Chem.* **1984**, *49*, 1494.
(19) Stahly, G. P.; Stahly, B. C.; Lilje, K. C. *J. Org. Chem.* **1984**, *49*, 578.

SCHEME 7. VNS Reactions with 6-Nitroquinoline



independent reaction pathway for the formation of this compound. Regardless of the base employed the initial attack of the nucleophile leads to σ-adduct **A**. In the case of potassium *tert*-butoxide a fast deprotonation of the σ-adduct **A** leads to elimination to the VNS product **5**. However, deprotonation with sodium hydride in DMF is kinetically slower and therefore the σ-adduct may collapse by attack of the nitronate oxygen onto the carbonyl function of the ester. Elimination of hydrochloric acid leads to intermediate **C**, which can undergo deprotonation to *o*-nitrosocarbene **D**, leading to isoxazole **17** via an electrocyclization process. A similar mechanism for the formation of a fused isoxazole has been previously postulated in the literature.[20]

Another interesting divergence from the standard VNS pathway has recently been reported by Tomioka in the reaction of 6-nitroquinoline (**9**) with ethyl chloroacetate in the presence of sodium hydride (Scheme 7).[21] With THF as solvent the reaction proceeds through the same mechanism as with potassium *tert*-butoxide as base, and the VNS product **18** (44%) is obtained as the major product. Switching to DMF as solvent, however, led to the formation of a new product in reasonable yield (51%). The structure of this product was assigned by Tomioka as dihydroisoxazolo[4,3-*f*]quinoline *N*-oxide **19** based on ^{1}H NMR and IR data.

Having observed the novel reactivity under slightly modified VNS conditions for 5-nitroisoquinoline (**3**) we decided to reinvestigate the reaction of 6-nitroquinoline (**9**) under these conditions (Scheme 7). The addition of sodium hydride to a mixture of 6-nitroquinoline (**9**) and ethyl chloroacetate in DMF, followed by a quench with ammonium chloride led to three distinct products. One species was identified as VNS product **18**.[22] The two other products were obtained as a chromatographically inseparable mixture. The ^{1}H NMR and MS data of this mixture were identical with the data that Tomioka had reported for compound **19**. However, we noticed a characteristic IR band at 1538 cm^{-1}, suggesting that the nitro-group was retained in the product. Additional NMR analysis, including ^{13}C NMR, HMBC, COSY, and ^{1}H$-^{15}$N correlation, was also inconsistent with the connectivity proposed in the literature. We were able to assign the structure of the product as nitrocyclopropane **20**, which was obtained as a 1:1.3 mixture of cis$-$trans isomers. A single crystal from this mixture was determined to be the trans-isomer **20a** by X-ray diffraction (Figure 1). A mechanism for this novel cyclopropanation reaction proceeds through the intermediate shown in Scheme 7. Initial attack of the nucleophile leads to the σ-adduct **E**. In THF as solvent the deprotonation is kinetically faster and the intermediate undergoes elimination to the VNS product **18**. Apparently the second deprotonation is kinetically slower with sodium hydride in DMF and a significant amount of the intermediate can undergo simple cyclization by *C*-alkylation of the nitronate. The previously proposed *O*-alkylation, leading to product **19**, is not observed.[21] A similar formal cyclopropanation reaction was recently reported for nitroolefins,[23] but we are unaware of any examples of direct cyclopropanations of nitroaromatic compounds. The reasons for the mechanistic dichotomy in the reactions of **3** and **9** are currently unclear and will be the subject of further investigation.

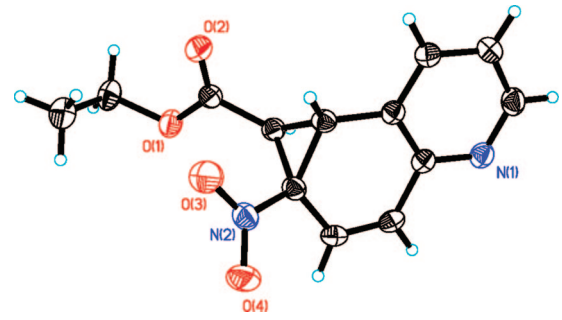


FIGURE 1. Solid-state structure of nitrocyclopropane **20a**.

Summary

An efficient approach for the synthesis of 6-methyl-5-nitroisoquinoline (**1**) was developed. It relies on a one-pot three-step approach (VNS reaction with ethyl chloroacetate, saponification, decarboxylation) starting from 5-nitroisoquinoline. The reaction is applicable to several other heterocyclic scaffolds. In the course of our studies we also discovered two new reaction pathways under VNS conditions. Reaction with ethyl chloroacetate in the presence of sodium hydride in DMF leads to the formation of an isoxazole in the case of 5-nitroisoquinoline and to the formation of a nitrocyclopropane in the case of 6-nitroquinoline.

Experimental Section

6-Methyl-5-nitroisoquinoline (1) (via a two-pot process). Under nitrogen, potassium *tert*-butoxide (70.9 g, 0.619 mol, 2.20 equiv)

(20) Duffy, K. J.; Tennant, G. *J. Chem. Soc., Chem. Commun.* **1995**, 2457.
(21) Maruoka, H.; Tomioka, Y. *J. Heterocycl. Chem.* **2003**, *40*, 1051.
(22) Identified by LC/MS and crude ^{1}H HMR.
(23) McCooey, S. H.; McCabe, T.; Connon, S. J. *J. Org. Chem.* **2006**, *71*, 7494.

was dissolved in THF (225 mL) and the reaction mixture was cooled to −10 °C. A solution of 5-nitroisoquinoline (**3**) (50.0 g, 0.281 mol, 1.00 equiv) and ethyl chloroacetate (33.31 mL, 0.309 mol, 1.10 equiv) in THF (300 mL) previously prepared at rt was added dropwise within 1.5 h (exothermic addition). The mixture was stirred for an additional 2 h at $-10 < T < 0$ °C and water (500 mL) was slowly added over 0.5 h at <10 °C (mildly exothermic). The reaction mixture was stirred under nitrogen for 18 h to saponify the ethyl ester. The VNS reaction after saponification was monitored by HPLC and showed 4.2% of the remaining 5-nitroisoquinoline. To the resulting black solution was added isopropyl acetate (250 mL) at 20−25 °C and the reaction mixture was decanted. The aqueous phase was re-extracted with isopropyl acetate (250 mL) to eliminate the remaining 5-nitroisoquinoline. Activated carbon L3S (2.5 g) was added to the aqueous phase and the resulting mixture was stirred for 1 h at 20−25 °C. The mixture was filtered and washed with water (2 × 25 mL). The basic filtrate was neutralized to pH 3 with 5 N HCl (60 mL) and the resulting suspension was stirred for 3 h at 0−5 °C. The resulting solid was filtered, washed with water (2 × 100 mL), ethanol (50 mL), and heptane (50 mL), and dried at 20 °C under vacuum to give 58.1 g of (5-nitroisoquinolin-6-yl)acetic acid **6** (88.9% yield, 92.4% of **6** and 6.5 of **1** by HPLC). A 25.0 g (0.108 mol, 1.00 equiv) sample of this crude product was suspended in dimethylformamide (75 mL). Potassium carbonate (14.9 g, 0.108 mol, 1.00 equiv) was added and the mixture was stirred at 20−25 °C for 3 h. Water (375 mL) was added and the resulting suspension was aged for 18 h. The precipitate was collected by filtration, washed with water (50 mL), and dried at 60 °C under vacuum to give 15.4 g (76.1%) of 6-methyl-5-nitroisoquinoline (**1**) as a clear brown powder. Mp 135−137 °C (EtOAc/hexanes); IR 1631, 1589, 1565, 1510, 1480, 1380, 1344, 1276, 1231, 1222, 1161, 1014, 872, 825, 812, 802 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm) 9.46 (1H, s), 8.66 (1H, d, $J = 6.0$ Hz), 8.35 (1H, d, $J = 8.5$ Hz), 7.77 (1H, d, $J = 8.5$ Hz), 7.61 (1H, d, $J = 5.5$ Hz), 2.55 (3H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 152.5, 145.6, 145.2, 133.4, 131.0, 130.3, 126.7, 126.6, 113.4, 17.8; HRMS (*m*/*z*) [M + H^+] calcd for $(C_{10}H_9N_2O_2)^+$ 189.0659, found 189.0658.

6-Methyl-5-nitroisoquinoline (1) (via a one-pot process). Under nitrogen, potassium *tert*-butoxide (70.9 g, 0.619 mol, 2.20 equiv) was dissolved in THF (225 mL) and the reaction mixture was cooled to −10 ± 5 °C. A solution of 5-nitroisoquinoline (**3**) (50.0 g, 0.281 mol, 1.00 equiv) and ethyl chloroacetate (33.3 mL, 0.309 mol, 1.10 equiv) in THF (300 mL) previously prepared at 20−25 °C was added dropwise within 3 h to maintain <3 °C (exothermic addition). The mixture was stirred for an additional 4 h at <0 °C and water (500 mL) was slowly added over 35 min at <10 °C (mildly exothermic). The reaction mixture was stirred under nitrogen overnight to saponify the ethyl ester. The VNS reaction after saponification was monitored by HPLC and showed <0.5% of the remaining 5-nitroisoquinoline. To the resulting black solution was added isopropyl acetate (250 mL) at 20−25 °C and the reaction mixture was decanted. The aqueous phase was re-extracted with isopropyl acetate (250 mL) to eliminate the remaining 5-nitroisoquinoline. Activated carbon L3S (2.5 g) was added to the aqueous phase and the resulting mixture was stirred for 1 h at 20−25 °C. The mixture was filtered and washed with water (2 × 10 mL). The basic media was neutralized to pH 0.5 with 5 N HCl (114 mL) and the resulting solution was heated to 90 ± 5 °C for 6 h. Residual isopropyl acetate and THF from the two extractions in basic media were eliminated by distillation during heating. Activated carbon L3S (3.27 g,) was added to the mixture previously cooled to 20−25 °C. After being stirred for 1 h, the mixture was filtered and washed with water (2 × 5 mL). The aqueous filtrate was neutralized to pH 4 with 5 N NaOH (60 mL) under cooling to 0 ± 5 °C. The resulting suspension was filtered, washed with water (2 × 65 mL) to remove minerals, and dried at 60 °C under vacuum to give 39.92 g (75.4%) of 6-methyl-5-nitroisoquinoline (**1**) as a clear brown powder.

Ammonium 2-Oxa-1,7-diazabenz[*e*]indene-3-carboxylate (17). Under nitrogen, 5-nitroisoquinoline (**3**) (3.56 g, 20.0 mmol, 1.00 equiv) and ethyl chloroacetate (6.42 mL, 60.1 mmol, 3.00 equiv) were dissolved in dry DMF (60 mL) and cooled to −13 °C in an acetone/ice bath. A 60% suspension of sodium hydride in mineral oil (2.48 g, 62.1 mmol, 3.11 equiv) was added in one portion with stirring. After the initial 5 min at −13 °C the reaction mixture fairly rapidly warmed (reached −7 °C). The internal temperature slowly warmed to −2 °C over 15 min, and then started dropping back again. At this point a complete conversion was observed by HPLC. Water (0.10 L) precooled to ca. 0 °C was added in one portion to afford a thick orange slurry. The resulting suspension was filtered at room temperature. The filtercake was rinsed with acetone and air-dried to afford the title compound **17** as an orange powder (2.78 g, 59% yield). Mp >400 °C (loss of NH_3 around 250 °C); IR 2636, 1703, 1600, 1543, 1498, 1454, 1387, 1297, 1120, 1027, 953, 854, 794, 707 cm^{-1}; ^1H NMR (DMSO-d_6, 600 MHz) δ (ppm) 8.85 (1H, s), 8.46 (1H, d, $J = 5.4$ Hz), 8.07 (1H, d, $J = 5.4$ Hz), 7.48 (1H, d, $J = 9.1$ Hz), 7.17 (4H, s), 6.79 (1H, d, $J = 9.1$ Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm) 167.9, 159.9, 149.7, 147.8, 145.0, 131.9, 129.3, 124.2, 116.4, 114.1, 108.6; HRMS (*m*/*z*) [M − NH_4^-] calcd for $(C_{11}H_5N_2O_3)^-$ 213.0306, found 213.0268.

Ethyl 1a-Nitro-1a,3a,7a,7b-tetrahydro-1*H*-4-aza-cyclopropa[*a*]-naphthalene-1-carboxylate (20a/20b). The literature protocol[21] was followed. Under nitrogen, 6-nitroisoquinoline (**9**) (3.56 g, 20.0 mmol, 1.00 equiv) and ethyl chloroacetate (6.42 mL, 60.1 mmol, 3.00 equiv) were dissolved in dry DMF (60 mL) and cooled to −11 °C in an acetone/ice bath. A 60% suspension of sodium hydride in mineral oil (2.48 g, 62.1 mmol, 3.10 equiv) was added in one portion with stirring. Immediately the reaction mixture became green. Some minor off-gassing and a slight temperature change was observed. The reaction mixture was allowed to react at −12 to −10 °C for 1 h upon which it gradually turned into a dark-orange nonviscous solution. At this point a complete conversion was observed by HPLC to three products: **20a** (major), **20b** (major), and **18** (minor). The reaction mixture was allowed to reach 2 °C over 1 h, then was cooled to −10 °C. Water (0.10 L) precooled to ca. 0 °C was added in one portion to afford a dark orange-red solution. The reaction mixture was extracted with $CHCl_3$ (50 mL) and the organic layer was stripped under vacuum to a crude dark brown liquid. Chromatography on silica (hexanes:EtOAc 6:4) afforded a VNS product **18**[21] as a dark-colored semisolid (0.14 g, 3% yield) and a mixture of diastereoisomers **20a** and **20b** as an orange oil (0.97 g, 19% yield). ^1H NMR spectrum of this mixture is in agreement with the previously reported spectrum.[21] IR 1733, 1538, 1448, 1354, 1316, 1262, 1182, 1026, 784, 722 cm^{-1}. **20a**: ^1H NMR (DMSO-d_6, 600 MHz) δ (ppm) 8.56 (1H, dd, $J = 5.2$, $J = 1.9$ Hz), 8.12 (1H, d, $J = 7.6$ Hz), 7.40 (1H, dd, $J = 7.8$ Hz, $J = 4.8$ Hz), 7.10 (1H, dd, $J = 10.2$ Hz, $J = 1.7$ Hz), 6.83 (1H, d, $J = 10.2$ Hz), 4.33 (1H, dd, $J = 6.8$ Hz, $J = 1.9$ Hz), 4.19 (1H, dq, $J = 10.9$ Hz, $J = 7.1$ Hz), 4.16 (1H, dq, $J = 10.9$ Hz, $J = 7.1$ Hz), 2.10 (1H, d, $J = 6.8$ Hz), 1.21 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm) 167.7, 149.5, 148.1, 137.3, 130.1, 126.3, 123.8, 123.4, 120.2, 69.9, 62.3, 29.6, 14.4; ^{15}N NMR (DMSO-d_6, 61 MHz) δ (ppm) 379.0, 314.4. **20b**: ^1H NMR (DMSO-d_6, 600 MHz) δ (ppm) 8.52 (1H, dd, $J = 4.7$ Hz, $J = 1.6$ Hz), 8.00 (1H, d, $J = 7.9$ Hz), 7.38 (1H, dd, $J = 7.7$ Hz, $J = 4.8$ Hz), 6.97 (1H, dd, $J = 10.2$ Hz, $J = 1.5$ Hz), 6.88 (1H, d, $J = 10.2$ Hz), 4.30 (1H, dd, $J = 11.3$ Hz, $J = 1.5$ Hz), 3.86 (1H, d, $J = 11.3$ Hz), 3.85 (1H, dq, $J = 10.8$ Hz, $J = 7.1$ Hz), 3.81 (1H, dq, $J = 10.8$ Hz, $J = 7.1$ Hz), 0.90 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (DMSO-d_6, 150 MHz) δ (ppm) 163.5, 149.6, 149.0, 137.4, 130.6, 124.9, 124.8, 120.2, 66.7, 61.2, 34.7, 24.5, 14.1; ^{15}N NMR (DMSO-d_6, 61 MHz) δ (ppm) 383.2, 312.3. HRMS (*m*/*z*) [M + H^+] calcd for $(C_{13}H_{13}N_2O_4)^+$ 261.08698, found 261.08762.

Recrystallization of the mixture of **20a** and **20b** from EtOAc/hexanes afforded crystals of **20a** suitable for a single-crystal X-ray diffraction analysis. Mp 95 °C (EtOAc/hexanes).

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **8**, **10**, **12**, **14**, **16**, **17**, and **20**, experimental procedures and characterization data for **1**, **5**, **6**, **8**, **10**, **12**, **14**, and **16**, details about structure elucidation for compounds **20a/b**, and X-ray crystallographic data for compound **20a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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