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AN EFFICIENT SYNTHESIS OF 3-NITROPYRROLES [1]

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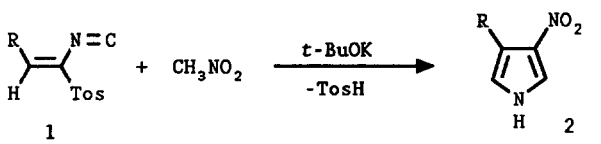
Abstract: 3-Nitropyrroles are synthetically accessible in high yield from nitromethane and 1-isocyano-1-tosyl-1-alkenes (**1**), in one single operation.

In a recent paper on the synthesis of pyrroles, Barton, Kervagoret and Zard have discussed the virtues of conjugated nitroolefins as substrate molecules in pyrrole ring constructions.[2] They obtained pyrroles by base-induced addition of α-isocyanoacetic esters or tosylmethyl isocyanide (TosMIC) to nitroolefins via a tandem of Michael addition and ring closure between the isocyano and enolate carbons, followed by an aromatizing elimination. In these processes pyrrole ring systems are formed by a "CNC—C_2 Cyclization".[3] We previously have reported the related synthesis of pyrroles from Michael acceptors of type R-CH=CH-Z (with Z = COR, COOR, C≡N) and TosMIC.[4]

Table. Pyrroles Synthesized According to Eq 1:

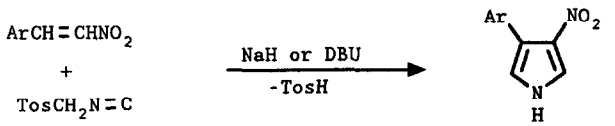


1 2 (Eq 1)

	R	Yield (%)	Mp (°C)
2a	C_6H_5	94	154-155
2b	p-ClC_6H_4	86	161-163
2c	p-$MeOC_6H_4$	88	155-156
2d	t-Bu	91	156-157

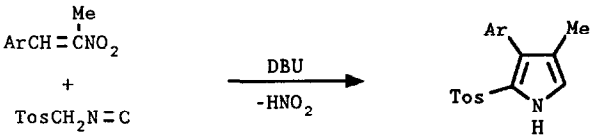
Use of nitroolefins as Michael acceptors brings a new element into the synthesis of pyrroles based on TosMIC. The kind of pyrrole that will be formed depends critically on the Cα-substituent in the nitroolefin. In Eqs 2 and 3 we have reproduced the (only) two examples (*i.e.* **2e** and **3**) reported in this context in the Zard paper.[2] In the final pyrrole-forming aromatization step HNO_2 is eliminated to give a 2-tosylpyrrole provided that Cα of the nitroolefin does not bear a hydrogen (Me in Eq 3), whereas TosH is eliminated to give a 3-nitropyrrole when Cα carries a hydrogen (Eq 2).[5]

Despite the low yields of nitropyrroles **2** obtained according to Eq 2, this process is important because it is the only direct method to form 3-nitropyrroles with unsubstituted 2 and/or 5 positions.[6] To quote Zard:[2] ".....this condensation (to **2e**) can serve after further improvement as an entry into 3-nitropyrroles which are only accessible with difficulty by other routes". We are offering the necessary improvement here.



(Eq 2)

2a 27% (Ar = Ph, this paper)
2e 14% (Ar = 4-MeO-3-($PhCH_2O$)C_6H_3; not optimized)[2]



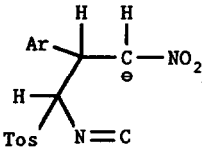
(Eq 3)

3 53% (Ar = *p*-MeC_6H_4)[2]

3-Nitropyrroles are formed in high yield by reaction of nitromethane with 1-isocyano-1-tosyl-1-alkenes (**1**) and *t*-BuOK in 1,2-dimethoxyethane (Eq 1 and Table). This alternative is superior to reactions based on nitroolefins (Eq 2), and derives from the

consideration that the nitroolefin substrate of Eq 2 is (formally) a condensation product of nitromethane and an aldehyde. This means that the pyrrole ring basically is put together from <u>three</u> reaction partners: the C5NC2 fragment from TosMIC and the C3 and C4 fragments from nitromethane and aldehyde (altogether a CNC—C—C Cyclization[3]). As we have already shown earlier in related imidazole syntheses, two different sequences exist in which one can bring the three reaction partners together.[7] When applied to the pyrrole case these two sequences would be: (1) combination of the C3 and C4 fragments to form a nitroolefin, followed by reaction with TosMIC (as in Eq 2); (2) initial condensation of TosMIC and an aldehyde to form the C4C5NC2 unit (*i.e.* compound **1**), followed by addition of the C3 fragment in the form of nitromethane. The latter process, that is base-mediated reaction of nitromethane with **1**, is subject of this paper (Eq 1, Table); the synthesis of 1-isocyano-1-tosyl-1-alkenes (**1**) is by now well documented in previous papers of our group.[7a,8]

In our hands the synthesis of 3-nitro-4-phenylpyrrole (**2a**), according to Eq 2, from β-nitrostyrene and TosMIC was achieved in 27% yield only.[9] When, however, **2a** was prepared according to Eq 1 (Table) the yield was 94%. Since both processes (Eq 1 and 2) are assumed to have **4** as a common (and probably important) intermediate,[5] it is not clear as to why such large differences in yield are observed. We tentatively, suggest that differences in stability between compounds **1** and nitroolefins under the basic conditions of reaction could play a role.



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Experimental Section

General. All reactions were carried out under nitrogen. ^{1}H NMR spectra were recorded on a 60-MHz Hitachi Perkin-Elmer R-24B apparatus. Melting points, taken in a silicone-oil bath, are uncorrected. Elemental microanalyses were carried out in our Analytical Department under the supervision of *Mr. A.F. Hamminga.*

3-Nitro-4-phenylpyrrole (**2a**, *According to Eq 1*). To a solution of nitromethane (0.11 mL), 2.0 mmol) in 5 mL of 1,2-dimethoxyethane (DME) at 0 °C was added *t*-BuOK (0.160 g, 1.4 mmol). After stirring for 15 min at 20 °C, a solution of 1-isocyano-2-phenyl-1-tosylethene[7a,8a] (**1a**, 0.283 g, 1.0 mmol) in DME (5 mL) was added in 10 min. After stirring for 1 h at 20 °C, the mixture was poured into 80 mL of icewater. The solid was collected, washed with water and dried in vacuum to give 0.177 g (94%) of **2a**, mp 148-152 °C. Crystallization from $CHCl_3$ raised the melting point to 150-152 °C; Mixed mp with material obtained from β-nitrostyrene and TosMIC (below) showed no depression. IR (Nujol) 3410 (NH), 1528 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 6.73 (triplet-like signal, J = 2 Hz, 1), 7.43 (s, 5), 7.76 (triplet-like signal, J = 2 Hz, 1), 8.6 (br. signal, 1).

(*According to Eq 2*). A mixture of TosMIC (6.6 g, 33 mmol), β-nitrostyrene (4.5 g, 30 mmol), ether (15 mL) and DMSO (65 mL) was added over 25 min to a stirred suspension of NaH (50% dispersion in mineral oil, 1.8 g, 36 mmol) in ether (30 mL). The mixture was refluxed for 1 h, then poured in 0.8 L of ice-water. The aqueous solution was acidified with 20 mL 2N HCl. The solid was collected, dried and filtered through activated coal with benzene. The filtrate was concentrated and the residue crystallized twice from benzene/petroleum ether (bp 40-60 °C) to give 1.5 g (27%) of **2a**, mp 153-155 °C. Analytically pure **2a** was obtained after three additional crystallizations from benzene petroleum ether (bp 40-60°C), mp 154-155 °C. Anal. Calcd for $C_{10}H_8N_2O_2$ (188.188): C, 63.83; H, 4.29; N, 14.89. Found: C, 64.09; H, 4.34; N, 14.60.

3-Nitro-4-(*p*-chlorophenyl)pyrrole (**2b**). To a suspension of *t*-BuOK (1.60 g, 14 mmol) in DME (40 mL) at 0 °C was slowly added from a syringe 1.1 mL (20 mmol) of nitromethane. After stirring for 15 min at 20 °C, a solution of 1-isocyano-2(*p*-chlorophenyl)-1-tosylethene [8a] (**1b**, 3.18 g, 10.0 mmol) in DME (40 mL) was added in 15 min. The mixture was stirred for 45 min, then poured in ice-water to give 1.91 g (86%) of **2b**. Analytically pure **2b** was obtained by sublimation (0.01 mm Hg) and one crystallization from $CHCl_3$, mp 161-163°C; IR (Nujol) 3430 (NH), 1528 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 7.03 (br. s, 1), 7.42 (br. s, 4), 7.98 (br. s, 1). Anal. Calcd for $C_{10}H_7ClN_2O_2$ (222.630): C, 53.95; H, 3.17; Cl, 15.92; N, 12.58. Found: C, 53.49; H, 3.18; Cl, 16.31; N, 12.50.

3-Nitro-4-(*p*-methoxyphenyl)pyrrole (2c) was prepared analogously to **2b** from 1-isocyano-2-(*p*-methoxyphenyl)-1-tosylethene[8a] (**1c**, 3.18 g, 10.0 mmol) in a yield of 1.92 g (88%), mp 143-150 °C. Analytically pure **2c** was obtained by two crystallizations from $CHCl_3$ and one sublimation (0.01 mm Hg, 140 °C), mp 155-156 °C; IR (Nujol) 3410 (NH), 1536 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 3.77 (s, 3), 6.56 (br. s, 1), 6.24, 6.38, 7.21 and 7.36 (AB-q, 4), 7.58 (br. signal, 1). Anal. Calcd for $C_{11}H_{10}N_2O_3$ (218.214): C, 60.55; H, 4.62; N, 12.84. Found: C, 60.36; H, 4.59; N, 12.87.

3-Nitro-4-*t*-butylpyrrole (2d) was prepared analogously to **2a** (*According to Eq 1*) from 3,3-dimethyl-1-isocyano-1-tosyl-1-butene[7a] (**1d**, 0.526 g, 2.0 mmol) in a yield of 0.305 g (91%), mp 148-154 °C. Analytically pure **2d** was obtained by sublimation (110 °C, 0.01 mm Hg) and two crystallizations from MeOH/water, mp 156-157 °C; IR (Nujol) 3400 (NH), 1520 cm^{-1} (NO_2); ^1H NMR ($CDCl_3$) δ 1.38 (s, 9), 6.55 (triplet-like signal, J = 2 Hz, 1), 7.75 (triplet-like signal, J = 2 Hz, 1), 8.9 (br. signal, 1). Anal. Calcd for $C_8H_{12}N_2O_2$ (168.197): C, 57.13; H, 7.19; N, 16.65. Found: C, 57.08; H, 7.20; N, 16.87.

References and Notes

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5. For proposed mechanisms, see refs. 2 and 4; Eq 2 follows the usual course of reaction leading to pyrroles as in ref 4.

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9. It remains to be seen whether the 14 % yield of **2e** as reported by Barton *et al.* can be much improved on optimization.[2]