Azide-Mediated Detosylation of *N*-Tosylpyrroloiminoquinones and *N*-Tosylindole-4,7-quinones

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Abstract: The utility of NaN_3 as a reagent for the detosylation of *N*-tosylpyrroloiminoquinones and *N*-tosylindole-4,7-quinones is described. The NaN_3-mediated detosylation is carried out in polar aprotic solvents such as DMF and DMSO. The reaction occurs under neutral, mild conditions and results in good to excellent yields of the detosylated quinones.

Key words: sodium azide, detosylation, quinones, indoloquinone, pyrroloiminoquinones.

Protection and deprotection strategies of reactive functional groups are extensively used in organic synthesis, particularly in multistep organic synthesis of natural products. Amine is a common reactive functional group, which often requires protection during an organic synthesis. Common protecting groups used for amines are carbamates and amides including sulfonamides.[1] Indole is a heterocyclic structural unit present in many biologically important organic molecules and natural products. More often, indole nitrogen needs to be protected during a synthesis.[2] The tosyl (*p*-toluene sulfonyl) group is a commonly used protecting group in the synthesis of indole and related alkaloids.[3,4] Removal of the tosyl group is often accomplished by using strongly basic reagents such as NaOH,[5] NaOMe, and thioglycolate.[6]

The tosyl group is particularly useful in protecting the N atom of present indoloquinones and pyrroloiminoquinones that are useful intermediates in the synthesis of many biologically active marine alkaloids.[7,8] Recently, pyrroloiminoquinone alkaloids have received increased attention for their anticancer activities.[9–12] A few important members of this alkaloid family are discorhabdins,[13] prianosins,[14] makaluvamines,[15] and isobatzellines.[16] This class of alkaloids has a unique tricyclic pyrroloiminoquinone ring structure.[15] The interesting fused three-ring structure coupled with potent biological properties such as topoisomerase II inhibition and cytotoxicities have made these alkaloids targets for a large number of synthetic studies.[17] Syntheses of these alkaloids involving several steps are reported in the literature. Many of these syntheses involve sensitive intermediates such as indole-4,7-quinones and pyrroloiminoquinones.[17] These synthetic intermediates almost always have a protection on the N atom of the quinone system. The tosyl group is one of the most commonly used N-protecting groups used in the synthesis of these alkaloids. A few such alkaloids are makaluvamine D,[18] discorhabdin C,[19] and secobatzelline B.[20] A few of *N*-tosylpyrroloiminoquinone and *N*-tosylindole-4,7-quinone intermediates reported in the synthesis of these marine alkaloids are given in Figure 1.

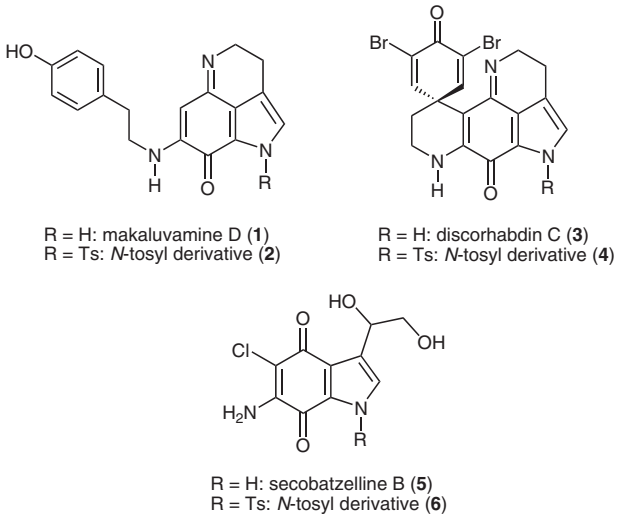

Figure 1 *N*-Tosyl-protected derivatives of pyrroloiminoquinone and indole-4,7-quinone alkaloids

Removal of the tosyl group (detosylation) from these intermediates is a key step in the syntheses of these alkaloids, which is often accomplished by the use of traditional reagents such as NaOH, NaOMe, NH_3, amines, etc. In Cava's synthesis of makaluvamine D detosylation is carried out by using amines.[18] In Heathcock's synthesis of discorhabdin C[7] synthesis and in Velu's synthesis of secobatzelline B[20] detosylation is carried out by using a stronger base (NaOMe).

As a part of our work on analogues of marine natural products with potential pharmacological value, we have been interested in studying the anticancer activity of makaluvamines and their analogues. We have synthesized makaluvamine analogues with substituents at the 7-position of the pyrroloiminoquinone ring and studied their effects on topoisomerase II inhibition and the anticancer activity.[21,22] The synthesis of makaluvamine analogues makes use of a reported[18] *N*-tosylpyrroloiminoquinone as a key intermediate from which desired compounds were prepared by

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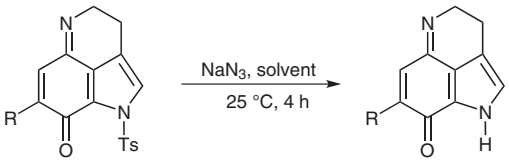
substitution with appropriate amines. After the introduction of substituents at the 7-position, we needed to detosylate the intermediates to obtain the final products of our interest. Our detosylation reactions of these intermediates using traditional reagents (NaOH, NaOMe, and NH_4OH) were complicated by the formation of side products and always resulted in low yields. Similar difficulties in detosylation of *N*-tosylpyrroloiminoquinones have been reported in the past in the case of a pyrroloiminoquinone alkaloid analogue synthesis.[23] In this particular literature report, the detosylation was carried out in 5–20% yields using the reagent TBAF.[23] To circumvent this problem, we were interested in developing more effective methods for detosylation that could work under milder reaction conditions.

While experimenting for milder reaction conditions for detosylation of *N*-tosylpyrroloiminoquinones, we have discovered that treatment of *N*-tosylpyrroloiminoquinone **7a** with sodium azide in DMF effected this deprotection very efficiently in good yields (83%) to afford the product **8a** (Table 1). The byproduct, *p*-toluenesulfonyl azide, formed in this reaction was also isolated and characterized.

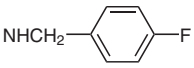
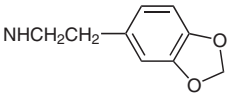
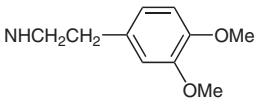
This detosylation reaction was very clean yielding only the expected product. The reaction is carried out at room temperature under mild conditions. It does not require strongly basic reaction conditions as the commonly used reagents. Sodium azide is a neutral reagent making it especially useful for the deprotection of *N*-tosylpyrroloiminoquinones containing base-sensitive groups. We also have examined the detosylation of other 7-amino-substituted pyrroloiminoquinones **7b–d** in a variety of polar protic, polar aprotic, and nonpolar solvents. The deprotection proceeded well in highly polar aprotic solvents such as DMF and DMSO (Table 1, entries 1–3, 6, 7, and 9, in 64–98% yield). The reaction did not work in a less polar solvent such as THF in the case of a 4-fluorobenzyl derivative (entry 5). In the case of dimethoxyphenethyl derivative the reaction in THF worked in poor yield taking longer reaction time (entry 11, 30%, 48 h). In polar protic solvent such as MeOH the reaction took longer time (48 h) yielding moderate yields (entries 4 and 10). Nonpolar solvents such as hexane was not favored for this reaction (entries 8 and 12).

To examine the generality of this detosylation procedure, we extended the study to a series of *N*-tosylindole-4,7-quinones. The results of azide-mediated detosylation of *N*-tosylindole-4,7-quinones are summarized in Table 2. All detosylation reactions of *N*-tosylindole-4,7-quinones using NaN_3 in polar aprotic solvents worked well with the purified yield of the products ranging from 82–98%. The reaction is favored in highly polar aprotic solvents such as DMF and DMSO as shown in the cases of several examples in Table 2. The reaction does not work in polar protic solvents (MeOH, entries 5 and 16), less polar aprotic solvents (THF, entries 8 and 14), or nonpolar solvents (hexanes, entry 20). Reactions in solvents such as MeOH and THF were also attempted at reflux temperatures without

Table 1 Sodium Azide Mediated Detosylation of *N*-Tosylpyrroloiminoquinones in *N*,*N*-Dimethylformamide



7a–d **8a–d**

Entry	7, 8	R	Solvent	Time (h)	Yield[a] (%)
1	**a**	OMe	DMF	4	83
2			DMF	4	84
3	**b**		DMSO	4	64
4			MeOH	48	25
5			THF	48	NR[b]
6			DMF	4	98
7	**c**		DMSO	4	74
8			hexane	48	NR[b]
9			DMF	4	88
10	**d**		MeOH	48	53
11			THF	48	30
12			hexane	48	NR[b]

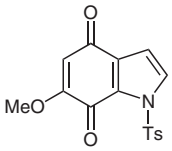
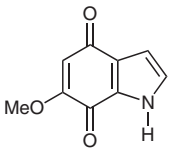
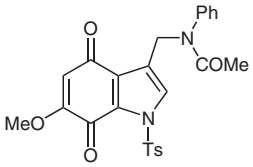
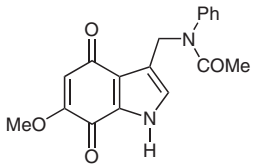
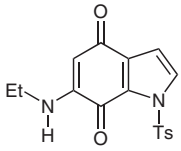
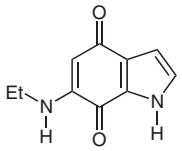
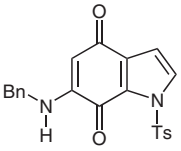
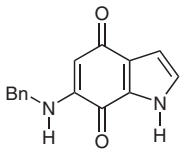
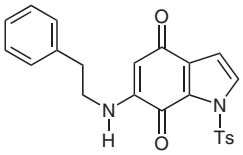
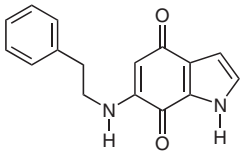
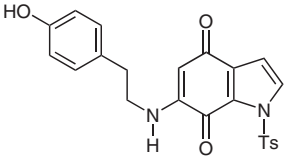
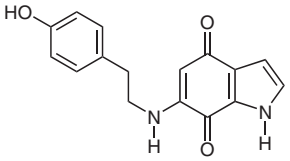
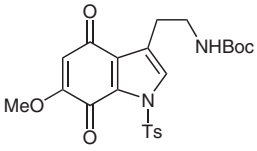
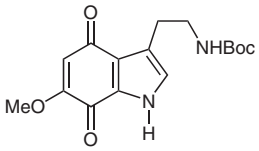
[a] Isolated yields.
[b] NR = no reaction.

resulting in the expected deprotection (entries 15 and 17). We have also noticed that the reaction is not moisture sensitive. It works in moist solvents just as well as in anhydrous solvents (entries 3, 4, and 12). Detosylation can be carried out selectively in the presence of other protecting groups such as *N*-Ac (entries 6 and 7) and *N*-Boc (entry 23) groups.

This NaN_3-mediated detosylation is selective to quinone systems described here. It does not work for the deprotection of regular *N*-tosylindoles. For example, treatment of *N*-tosyl-4,6,7-trimethoxyindole (**9**) with NaN_3 in DMF at room temperature as well as at 100 °C for 12 hours did not result in detosylation (Table 3).

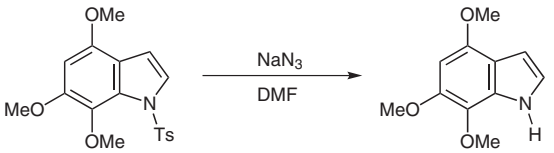
In conclusion, a novel efficient protocol for the detosylation of *N*-tosylpyrroloiminoquinones and *N*-tosylindole-4,7-quinones using a neutral reagent (NaN_3) has been discovered. The scope of this deprotection procedure is explored on a series of *N*-tosylpyrroloiminoquinone and *N*-tosylindole-4,7-quinone derivatives. The reaction is favored in highly polar aprotic solvents such as DMF and DMSO. It does not work or works in poor yields in polar protic or less polar solvents. The reaction does not work in nonpolar solvents. The reaction is selective to *N*-tosylindoloquinone systems. This detosylation procedure does not work for *N*-tosylindoles, and may therefore be used for the selective deprotection of *N*-tosylindoloquinone groups in the presence of other *N*-tosyl protecting groups. Further work is in progress to apply this methodology in the synthesis of several other makaluvamine analogues.

Table 2 Sodium Azide Mediated Detosylation of *N*-Tosylindole-4,7-quinones

Entry	Substrate	Solvent	Time (h)	Temp (°C)	Product	Yield (%)[a]
1		DMF	4	25	 **10**	82
2		DMSO	4	25		86
3		DMSO–H_2O	4	25		93
4		DMF–H_2O	4	25		91
5		MeOH	4	25		NR[b]
6		DMF	4	25	 **11**	92
7		DMSO	4	25		91
8		THF	4	25		NR[b]
9		DMF	4	25	 **12**	94
10		DMSO	4	25		83
11		DMF	4	25	 **13**	88
12		DMF–H_2O	4	25		91
13		DMSO	4	25		94
14		THF	4	25		NR[b]
15		THF	12	65		NR[b]
16		MeOH	4	25		NR[b]
17		MeOH	12	64		NR[b]
18		DMF	4	25	 **14**	94
19		DMSO	4	25		95
20		hexanes	4	25		NR[b]
21		DMF	4	25	 **15**	84
22		DMSO	4	25		82
23		DMF	4	25	 **16**	93

[a] Yields reported are of isolated products characterized by ^1H NMR and ^{13}C NMR spectroscopy.
[b] NR = no reaction.

Table 3 Attempted Detosylation of *N*-Tosyl-4,6,7-trimethoxy-indole *N*-Tosylindole Using NaN_3



9

Entry	Temp (°C)	Time (h)	Yield (%)
1	25	4	no reaction
2	100	12	no reaction

General Methods for Synthesis

Solvent evaporations were carried out in vacuo on a rotary evaporator. Thin layer chromatography (TLC) was performed on silica gel plates with fluorescent indicator (Whatmann, silica gel, UV254, 25 μm plates). Spots were visualized by UV light (λ = 254 and 365 nm). Purification by column and flash chromatography was carried out using 'BAKER' silica gel (40 μm) in the solvent systems indicated. Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Bruker DPX-300 spectrometer. The values of chemical shifts (δ) are given in ppm and coupling constants (*J*) in Hz. The chemical-shift values are reported as parts per million (ppm) relative to tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Micromass Platform LCC instrument. HRMS were recorded on AutoSpec-Ultima^{TM}NT instrument.

Detosylation of *N*-Tosylpyrroloiminoquinones – General Procedure

A solution of *N*-tosylpyrroloiminoquinone derivative (**7a**–**d**, 0.5 mmol) in DMF (2 mL) was stirred with NaN_3 (0.6 mmol, 1.2 equiv) at r.t. for 4 h. TLC examination (in 10% MeOH in $CHCl_3$) at this point revealed that the reaction is complete with the formation of only one new product spot. Solvent was completely removed under high vacuum, and the crude product was suspended in CH_2Cl_2. The precipitated solid was filtered to obtain the crude product. The crude product was further purified by column chromatography over silica gel to obtain the pure detosylated product **8a**–**d** in 83–98% yield. ^{1}H NMR, ^{13}C NMR, and MS spectral data of **8b**–**d** products were found to be identical to previously reported data.[22] Spectral data of compound **8a** are given below.

3,4-Dihydro-7-methoxypyrrolo[4,3,2-*de*]quinolin-8(1*H*)-one (8a)

^{1}H NMR (CD_3OD): δ = 3.05 (t, 2 H, *J* = 6.9 Hz), 3.22 (t, 2 H, *J* = 6.9 Hz), 3.83 (s, 3 H), 5.78 (s, 1 H), 7.10 (s, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 24.9, 40.7, 57.2, 108.4, 121.4, 124.7, 127.9, 131.7, 161.5, 172.6, 186.3 ppm. MS (ES^+): *m/z* = 204 [M + H]. HRMS (EI, 70 ev): *m/z* calcd for $C_{11}H_{10}N_2O_2$: 202.0742 [M^+]; found: 202.0741.

Detosylation of *N*-Tosylindole-4,7-quinones – General Procedure

A solution of *N*-tosylindole-4,7-quinone derivative (0.5 mmol) in DMF (2 mL) was stirred with NaN_3 (0.6 mmol, 1.2 equiv) at the temperature and solvent for a period indicated in Table 2. TLC examination (in 10% MeOH in $CHCl_3$) at this point revealed that the reaction is complete with the formation of only one new product spot. Solvent was completely removed under high vacuum, and the crude product was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with H_2O (3 × 10 mL) and brine (3 × 10 mL). Removal of solvent from the dried (Na_2SO_4) extract afforded the crude product, which was further purified by column chromatography over silica gel to obtain the pure detosylated products **10**–**16**.

6-Methoxy-1*H*-indole-4,7-dione (10)

^{1}H NMR (DMSO-d_6): δ = 3.77 (s, 3 H), 5.81 (s, 1 H), 6.47–6.49 (t, 1 H, *J* = 2.1 Hz), 7.25–7.27 (t, 1 H, *J* = 2.7 Hz), 12.75 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 56.9, 107.6, 107.7, 126.7, 128.1, 129.7, 160.4, 171.3, 183.5. MS (ES^+): *m/z* = 178 [M + H]. HRMS (EI, 70 ev): *m/z* calcd for $C_9H_7NO_3$: 177.0425 [M^+]; found: 177.0424.

***N*-[(6-Methoxy-4,7-dioxo-4,7-dihydro-1*H*-indol-3-yl)methyl]-*N*-phenylacetamide (11)**

^{1}H NMR (CD_3OD): δ = 1.78 (s, 3 H), 3.68 (s, 3 H), 5.00 (s, 2 H), 5.50 (s, 1 H), 7.02–7.07 (m, 3 H), 7.23–7.27 (m, 3 H). ^{13}C NMR (CD_3OD): δ = 21.2, 43.5, 55.7,106.8, 121.4, 126.9, 127.7, 127.8, 127.9, 129.2, 129.3 (2 C),142.4, 160.0, 171.5, 184.4. MS (ES^+): *m/z* = 325 [M + H].

6-(Ethylamino)-1*H*-indole-4,7-dione (12)

^{1}H NMR (DMSO-d_6): δ = 1.11–1.16 (t, 3 H, *J* = 7.2 Hz), 3.07–3.16 (p, 2 H, *J* = 7.2 Hz), 5.09 (s, 1 H), 6.38–6.39 (t, 1 H, *J* = 2.1 Hz), 7.06–7.10 (t, 1 H, *J* = 6 Hz), 7.21–7.23 (t, 1 H, *J* = 2.7 Hz), 12.59 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 13.4, 37.3, 96.2, 107.9, 128.5 (2 C), 129.2, 148.9, 172.4, 182.2. MS (ES^+): *m/z* = 191 [M + H]. HRMS (EI, 70 ev): *m/z* calcd for $C_{10}H_{10}N_2O_2$: 190.0742 [M^+]; found: 190.0738.

6-(Benzylamino)-1*H*-indole-4,7-dione (13)

^{1}H NMR (DMSO-d_6): δ = 4.35–4.37 (d, 2 H, *J* = 6.3 Hz), 5.00 (s, 1 H), 6.37 (s, 1 H), 7.22–7.33 (m, 6 H), 7.77–7.81 (t, 1 H, *J* = 6.3 Hz), 12.64 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 45.9, 97.6, 107.9, 127.4, 127.5 (2 C), 128.5 (2 C), 128.9 (2 C), 138.2, 148.9, 172.5, 182.2. MS (ES^+): *m/z* = 253 [M + H]. HRMS (EI, 70 ev): *m/z* calcd for $C_{15}H_{12}N_2O_2$: 252.0899 [M^+]; found: 252.0901.

6-(Phenethylamino)-1*H*-indole-4,7-dione (14)

^{1}H NMR (DMSO-d_6): δ = 2.87 (t, 2 H, *J* = 7.8 Hz), 3.33 (m, 2 H), 5.18 (s, 1 H), 6.40 (d, 1 H, *J* = 2.4 Hz), 7.11 (t, 1 H, *J* = 6.0 Hz), 7.20–7.31 (m, 7 H), 12.6 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 33.8, 44.0, 96.6, 107.9, 126.7, 128.4, 128.6, 128.9, 129.1, 129.2, 139.5, 148.8, 172.3, 182.2. MS (ES^+): *m/z* = 267 [M + H]. HRMS (EI, 70 ev): *m/z* calcd for $C_{16}H_{14}N_2O_2$: 266.1055 [M^+]; found: 266.1060.

6-(4-Hydroxyphenethylamino)-1*H*-indole-4,7-dione (15)

^{1}H NMR (CD_3OD): δ = 2.74 (t, 2 H, *J* = 7.8 Hz), 3.26 (t, 2 H, *J* = 7.0 Hz), 5.12 (s, 1 H), 6.40 (d, 1 H, *J* = 1.2 Hz), 6.63 (d, 2 H, *J* = 8.7 Hz), 6.97 (d, 2 H, *J* = 8.4 Hz), 7.03 (d, 1 H, *J* = 3.0 Hz). ^{13}C NMR (DMSO-d_6): δ = 32.8, 44.1, 95.1, 107.5, 115.0, 127.2, 128.2, 128.8, 129.2, 129.3, 149.6, 155.8, 171.2,184.4. MS (ES^+): *m/z* = 283 [M + H].

***tert*-Butyl 2-(4,7-Dihydro-6-methoxy-4,7-dioxo-1*H*-indol-3-yl)-ethylcarbamate (16)**

^{1}H NMR (DMSO-d_6): δ = 1.32 (s, 9 H), 2.75 (t, 2 H, *J* = 7.1 Hz), 3.12 (t, 2 H, *J* = 6.0 Hz), 3.75 (s, 3 H), 5.75 (s, 1 H), 6.83 (br s, 1 H), 7.06 (d, 1 H, *J* = 2.4 Hz), 12.57 (br s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 26.1, 28.6 (3 C), 56.8, 77.8, 79.7, 107.9, 123.3 (2 C), 126.6, 129.8, 155.9, 160.0, 171.0, 184.5. MS (ES^+): *m/z* = 305 [M + H]. HRMS (EI, 70 ev): *m/z* calcd for $C_{16}H_{14}N_2O_2$: 247.0719 [M – C_4H_9O]$^+$; found: 247.0717.

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