cine-Substitution of 1-Methyl-3,6,8-trinitro-2-quinolone

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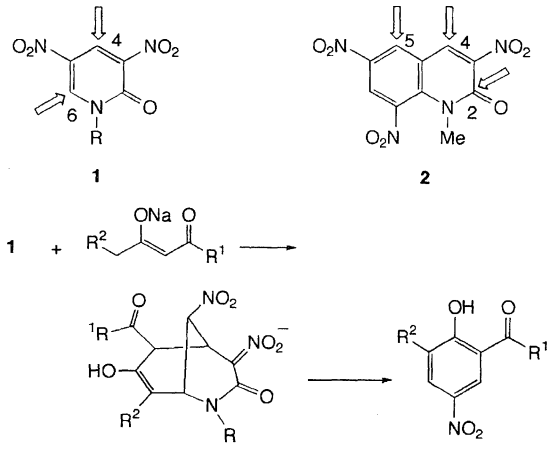
cine-Substitution of 1-methyl-3,6,8-trinitro-2-quinolone by 1,3-dicarbonyl compounds in the presence of NEt_3 occurred efficiently, affording 4-functionalized 6,8-dinitro-2-quinolone derivatives. The addition intermediate was isolated in the reaction with $CH_2(CO_2Et)_2$ and EtONa. Conversion of the isolated intermediate into the *cine*-substituted product was performed. These results indicate that the present *cine*-substitution proceeds by the addition-elimination mechanism.

1-Substituted 3,5-dinitro-2-pyridones **1**, highly electron deficient heteroaromatic compounds, have been found to be excellent precursors of various polyfunctionalized systems by ring transformation.[1] In these reactions, dinitro-2-pyridone **1** behaves as a synthetic equivalent of an unstable nitromalonaldehyde by the stepwise reaction with bidentate anions at the 4- and 6-positions.

Our interest was extended to the chemical behavior of fused 2-pyridones which have more widely conjugated systems. 1-Methyl-3,6,8-trinitro-2-quinolone (**2**) is regarded as an [*e*] fused benzopyridone,[2] of which the 8a-position, corresponding to the 6-position of the 2-pyridone ring is blocked by the fused benzene ring. Thus it is thought that the reactivity of the other points, such as 2-[2] or 5-positions,[3] could be utilized to give different skeletons. Namely, 2-quinolone **2** would be the equivalent of the α-nitrocinnamic acid derivative in the former case, and would be the precursor of tricyclic compound in the latter case (Scheme 1). The reactions of 2-quinolone **2** with several 1,3-dicarbonyl compounds were examined. The results we obtained were not those we had anticipated. We describe here interesting reactivity of **2**, which would be a novel functionalization method of the quinoline ring.



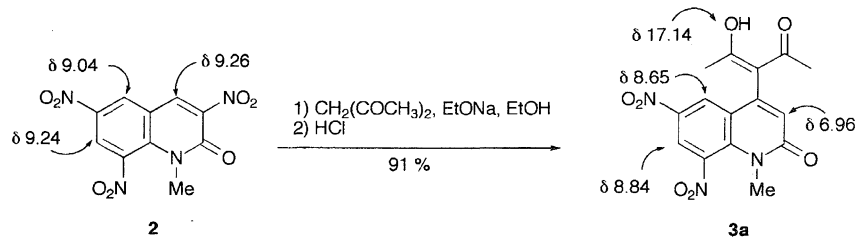
Scheme 1.

Results and Discussion

Treatments of trinitroquinolone **2** with Na salt of $CH_2(COCH_3)_2$ at room temperature gave yellow plates whose spectral data corresponded to those of neither a ring transformed product nor a tricyclic compound, which were the predicted products of the reaction. In the ^1H NMR, a singlet signal at $\delta = 6.96$ appeared in place of the disappearance of a singlet at $\delta = 9.26$ assigned to a proton at 4-position. It was also observed that protons of the benzene ring, a pair of doublets at $\delta = 9.04$ and 9.24, shifted to higher field. These observations mean that the enolate ion attacked only at the 4-position of 2-quinolone **2**, though the nucleophilic susceptibility[4] of the 5-position is almost same as that of the 4-position (4-position: 0.305, 5-position: 0.301). Analytical data for this product revealed that an HNO_2 was lost from the adduct of trinitro-2-quinolone **2** and $CH_2(COCH_3)_2$. Based on these facts, the product was identified as the *cine*-substituted quinolone **3a** (Scheme 2). Product **3a** is in the enol form only, because it is stabilized by a strong intramolecular hydrogen bond which shows a singlet signal at $\delta = 17.14$ in the ^1H NMR ($CDCl_3$ solution).

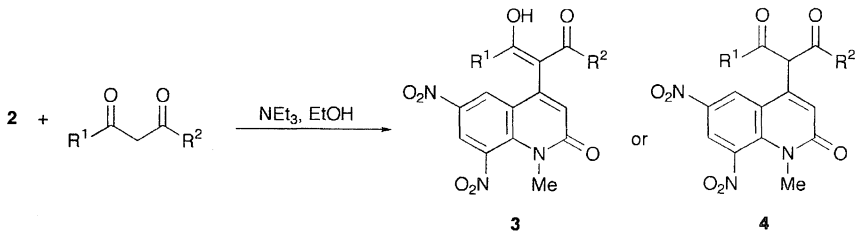
The present *cine*-substitution proceeded readily enough by the addition of NEt_3 to a mixture of 2-quinolone **2** and $CH_2(COCH_3)_2$ without any necessity of converting the diketone into the sodium enolate. Thus reactions with some other 1,3-dicarbonyl compounds were conducted with NEt_3. The cyclic diketone, keto esters and the diester also afforded *cine*-substituted 2-quinolone **3** or **4**. The 2-quinolone **3a**—**d** derived from diketones and keto esters existed in the enol forms. On the other hand, $CH_2(CO_2Et)_2$ gave the keto formed product **4e** (Scheme 3).

As **3c** was treated on SiO_2 column chromatography for purification, deacetylation[5] proceeded to furnish 2-quinolone **5** quantitatively. The same product **5** was obtained when **3d** was similarly treated. In this case, a small amount of the compound possessing a singlet signal at $\delta = 5.19$ in the ^1H NMR was additionally eluted. Compared with the NMR data of **4e**, the signal would be assigned to a methine proton of the keto form **4d**. Furthermore, the 2-quinolone **5** was not



2 **3a**

Scheme 2.



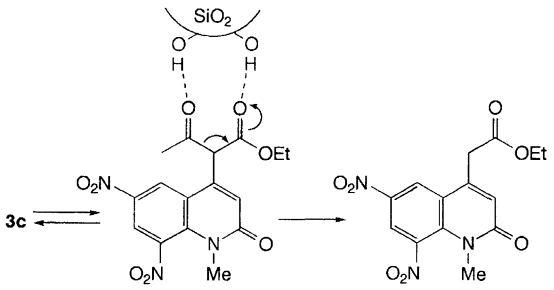
3 **4**

Scheme 3.

detected during the column chromatography of **3a**; therefore it was considered that **5** was produced after conversion of **3c** and **3d** into the keto forms **4c** and **4d** (Scheme 4).

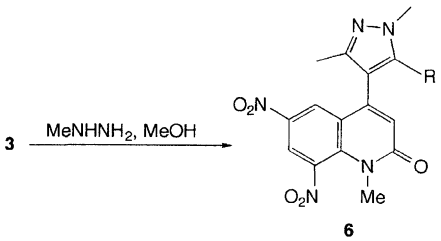
When ring closure on the introduced substituent was attempted, similar deacetylation was observed. *cine*-Substituted 2-quinolone **3a** was treated with $MeNHNH_2$ to afford 4-(4-pyrazolyl)-2-quinolone **6a**. But the product obtained from **3c** under the same conditions was not **6c** but the deacetylated product **5** (Scheme 5).

As mentioned above, the newly introduced substituents showed a remarkable difference in their tautomerism. These



4c **5**

Scheme 4.



6

R		Yield (%)
Me	**6a**	91
OH	**6c**	— [a]

[a] **5** was quantitatively obtained.

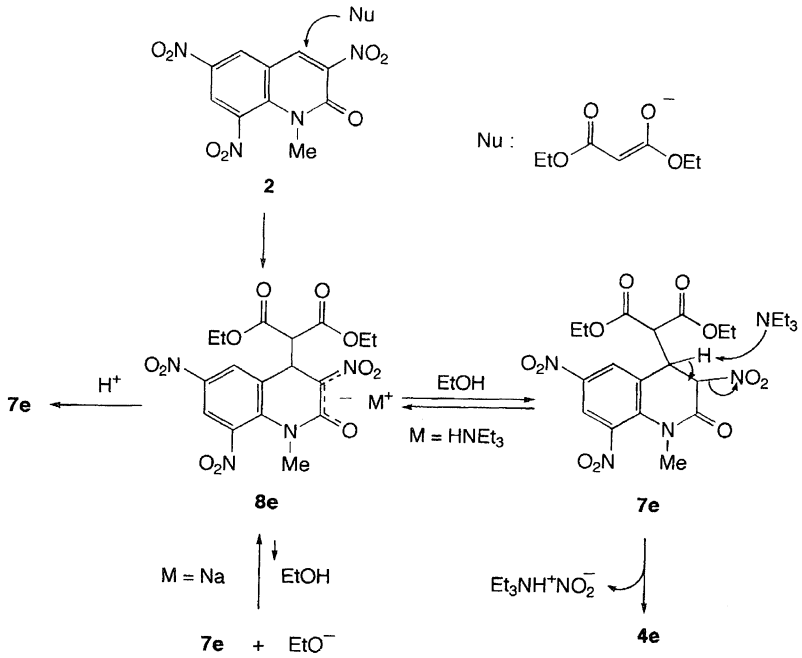
Scheme 5.

substituents did not have coplanality with the 2-quinolone ring owing to steric hindrance.[6] The calculated dihedral angle[4] between 2-quinolone ring and the substituent is 81.4° in the case of **3a**. So it was thought that the ease of enolization of the introduced substituents only depended upon stability of enol forms in 1,3-dicarbonyl compounds. Comparison of the heat of formation[4] shows that **4a** is more stable than **3a** (the difference is 1.03 kcal mol^{-1}) and **4e** is more stable than **3e** (3.67 kcal mol^{-1}).

When $CH_2(CO_2Et)_2$ was employed for *cine*-substitution, the ^1H NMR spectra of the reaction mixture suggested the presence of an intermediary adduct **7e** in addition to those of the *cine*-substituted product **4e**. Nevertheless, the product isolated after usual workups was **4e**, and the compound having the signals observed in the reaction mixture was not obtained. In various attempts to isolate the intermediate, the greater part of the product was the adduct **7e** when Na salt of $CH_2(CO_2Et)_2$ was used as a nucleophile. By treatment of the acidified reaction mixture on silica gel column chromatography, **7e** was isolated in 63% yield, together with recovery of starting material **2** (20%).

The adduct **7e** was thermally stable enough to be recrystallized from EtOH. Since a signal of H-4 was observed as a double doublet in the ^1H NMR, **7e** was suggested to be keto form in the solution. The coupling constant between the protons at the 3- and 4-positions was 2.6 Hz. Since the calculated dihedral angles[4] for *cis*- and *trans*-forms are 61.0° and 69.6° respectively, there is a possibility that the adduct **7e** is the *cis*-form. The isolated **7e** was treated with NEt_3 to give *cine*-substituted product **4e** in 86% yield. So the adduct **7e** was confirmed to be the intermediate of the present reaction.

The products varied with the bases employed. Namely, the adduct **7e** was predominantly obtained in the case of EtONa, and *cine*-substituted product **4e** was also yielded in the case of NEt_3. These facts are accounted for by pK_a values of **7e** and the two bases. Since the pK_a value of EtOH is much higher than those of the others, the anionic form **8e** is more stable than EtO^-. So the adduct **7e** was afforded with acidifying

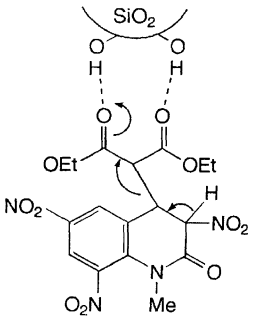


Scheme 6.

of the reaction mixture. On the other hand, the pK_a of **7e** may be similar enough to that of $HNEt_3^+$ for formation of a considerable amount of **7e** and NEt_3 in equilibrium. Then HNO_2 is eliminated[7] from the 3- and 4-positions to give *cine*-substituted 2-quinolone **4e**. In this manner, the present substitution proceeds in Michael type addition, followed by an elimination mechanism via the intermediate **7** (Scheme 6).

The more readily a substituent at the 4-position was enolized, the more easily elimination of HNO_2 from the intermediate **7** occurred to yield *cine*-substituted products. This result was due to steric repulsion of the enolized rigid substituents. In the silica gel column, deprotonation at the 3-position of **7e** occurred together with elimination of malonate to afford starting material **2** (Scheme 7).

Among several types of *cine*-substitution,[8,9] instances accompanying elimination of a nitro group were limited to dinitro systems.[9] In these reactions, the eliminating nitro group is activated with another nitro group at the vicinal position. On the other hand, the nitro group at the 3-position of 2-quinolone **2** is activated with the adjacent carbonyl group and the condensed benzene ring. Thus the present reaction offers a novel type reaction in the chemistry of nitro compounds.



Scheme 7.

The 1-methyl-2-quinolone skeleton is often found in alkaloids which are contained in Rutaceae family, and their biological activities have been energetically investigated.[10] From this point of view, development of convenient functionalization methods of the 2-quinolone ring is required. By utilizing the present reaction, a selective C–C bond formation at the 4-position of the 2-quinolone would be possible. Similar substitution by other various nucleophiles and further chemical transformation of synthesized *cine*-substituted 2-quinolone are now under investigation.

Experimental

All melting points were determined on a Yanaco micro melting point apparatus and were uncorrected. Elemental microanalyses were performed using a Yanaco MT-3 CHN corder and all values were within ±0.4% of the calculated values. IR spectra were recorded on a Horiba FT-200 infrared spectrometer and ^{1}H NMR spectra were obtained for solutions in $CDCl_3$ except for **3b** (DMSO-d_6) on a Hitachi NMR R-1200 at 60 MHz; chemical shifts are reported in ppm on the δ-scale from internal TMS. Column chromatography was conducted using Wako silica gel C-200 (100—200 mesh). The reaction was monitored by TLC performed on silica gel plates (Merck Art. 5715) with detection by UV light. All reagents and solvents were commercially available and were used as received. EtOH was dried over molecular sieves 4A for the reaction employing EtONa.

1-Methyl-3,6,8-trinitro-2-quinolone (2). Following the procedure described for 1-methyl-2-pyridone,[11] 2-quinolone was methylated and oxidized in the three times diluted solution to afford 1-methyl-2-quinolone in 86% yield: ^{1}H NMR δ = 3.71 (3H, s), 6.75 (1H, d, J = 9.7 Hz), 7.2—7.8 (5H, m). To cold fuming HNO_3 (d = 1.52, 10 mL), 1-methyl-2-quinolone (1.4 g, 9.7 mmol) was

gradually added and the mixture was heated at 120 °C for 7 h. Into the reaction mixture H_2O (100 mL) was poured. Crystalline precipitates were collected and recrystallized from PhH to give nitrated 2-quinolone **2** (1.61 g, 8.7 mmol, 90%) as yellow needles, mp 212—213 °C (lit,[12] 214—215 °C); IR (Nujol) 1678, 1532, 1345 cm^{-1}; ^1H NMR δ = 3.42 (3H, s), 9.04 (1H, d, J = 2.7 Hz), 9.24 (1H, d, J = 2.7 Hz), 9.26 (1H, s).

General Procedure for *cine*-Substitution Employing EtONa. To a solution of 2-quinolone **2** (295 mg, 1.0 mmol) and 1,3-dicarbonyl compound (1.2 mmol) in EtOH (30 mL), 0.15 M EtONa in EtOH (10 mL, 1.5 mmol, M = mol dm^{-3}) was added at room temperature over 30 min and the solution color became red. After being stirred for a further 3 h, the mixture was quenched with 1 M HCl (1 mL). EtOH was removed under reduced pressure, and the residue was extracted with $CHCl_3$ (30 mL×4). The organic layer was dried over ($MgSO_4$) and concentrated to afford the *cine*-substituted product **3** or the adduct **7e**. The products were purified by recrystallization or column chromatography.

General Procedure for *cine*-Substitution Employing NEt_3. To a solution of 2-quinolone **2** (295 mg, 1.0 mmol) and 1,3-dicarbonyl compound (1.2 mmol) in EtOH (30 mL), 0.05 M NEt_3 in EtOH (30 mL, 1.5 mmol) was added at room temperature over 30 min and the solution color turned orange. The reaction mixture was stirred for a further 3 h. After concentration, the reaction mixture was dissolved into $CHCl_3$ (20 mL) and washed with H_2O (20 mL) to remove Et_3NHNO_2. The organic layer was dried over ($MgSO_4$), and concentrated to afford the *cine*-substituted product **3** or **4**. The products were purified by recrystallization or column chromatography.

4-(1-Acetyl-2-hydroxy-1-propenyl)-1-methyl-6,8-dinitro-2-quinolone (3a): Purification by recrystallization from $CHCl_3$ afforded **3a** as yellow plates: Mp 248—249 °C; IR (Nujol) 1672 (br), 1525, 1333 cm^{-1}; ^1H NMR δ = 1.97 (6H, s), 3.59 (3H, s), 6.96 (1H, s), 8.65 (1H, d, J = 2.6 Hz), 8.84 (1H, d, J = 2.6 Hz), 17.14 (1H, s).

Found: C, 52.04; H, 3.69; N, 12.07%. Calcd for $C_{15}H_{13}N_3O_7$: C, 51.88; H, 3.77; N, 12.10%.

4-(2-Hydroxy-6-oxo-1-cyclohexenyl)-1-methyl-6,8-dinitro-2-quinolone (3b): As a *cine*-substituted product **3b** was precipitated during the reaction; the precipitate was filtered off and the filtrate was treated following the general procedure. Pale brown powder (not purified); mp > 300 °C; IR (Nujol) 1651, 1628, 1541, 1358 cm^{-1}; ^1H NMR δ = 1.8—2.3 (2H, m), 2.4—2.9 (4H, m), 3.42 (3H, s), 6.71 (1H, s), 8.37 (1H, d, J = 2.6 Hz), 8.97 (1H, d, J = 2.6 Hz), 8.5—12.0 (1H, br).

Found: C, 53.52; H, 3.65; N, 11.62%. Calcd for $C_{16}H_{13}N_3O_7$: C, 53.48; H, 3.65; N, 11.70%.

4-(1-Ethoxycarbonyl-2-hydroxy-1-propenyl)-1-methyl-6,8-dinitro-2-quinolone (3c): Purification by recrystallization from EtOH afforded **3c** as yellow needles: Mp 156—157 °C; IR (Nujol) 1678, 1645, 1527, 1345 cm^{-1}; ^1H NMR δ = 1.14 (3H, t, J = 7.0 Hz), 1.98 (3H, s), 3.58 (3H, s), 4.26 (2H, q, J = 7.0 Hz), 6.87 (1H, s), 8.60 (1H, d, J = 2.6 Hz), 8.81 (1H, d, J = 2.6 Hz), 13.51 (1H, s).

Found: C, 50.86; H, 3.99; N, 10.90%. Calcd for $C_{16}H_{15}N_3O_8$: C, 50.93; H, 4.01; N, 11.14%.

4-[1,3-Bis(ethoxycarbonyl)-2-hydroxy-1-propenyl]-1-methyl-6,8-dinitro-2-quinolone (3d): Purification by silica gel column chromatography (elution with 1 : 1 PhH–$CHCl_3$) afforded **3d** as yellow plates; mp 110—111 °C; IR (Nujol) 1732, 1676, 1657, 1525, 1342 cm^{-1}; ^1H NMR δ = 1.14 (3H, t, J = 7.0 Hz), 1.22 (3H, t, J = 7.0 Hz), 3.26 (2H, s), 3.55 (3H, s), 4.14 (2H, q, J = 7.0 Hz), 4.26 (2H, q, J = 7.0 Hz), 6.93 (1H, s), 8.65 (1H, d, J = 2.3 Hz), 8.80 (1H, d, J = 2.3 Hz), 13.2—13.7 (1H, br).

Found: C, 50.87; H, 4.10; N, 9.35%. Calcd for $C_{19}H_{19}N_3O_{10}$: C, 50.78; H, 4.26; N, 9.35%.

4-[Bis(ethoxycarbonyl)methyl]-1-methyl-6,8-dinitro-2-quinolone (4e): Purification by recrystallization from EtOH afforded **4e** as orange needles; mp 119—120 °C; IR (Nujol) 1732, 1676, 1527, 1340 cm^{-1}; ^1H NMR δ = 1.34 (6H, t, J = 7.3 Hz), 3.51 (3H, s), 4.37 (4H, q, J = 7.3 Hz), 5.14 (1H, s), 7.07 (1H, s), 8.83 (2H, brs).

Found: C, 49.94; H, 4.19; N, 9.99%. Calcd for $C_{17}H_{17}N_3O_9$: C, 50.13; H, 4.21; N, 10.32%.

4-[Bis(ethoxycarbonyl)methyl]-1-methyl-3,6,8-trinitro-3,4-dihydro-2(1*H*)-quinolinone (7e): Purification by column chromatography with $CHCl_3$ and by recrystallization from EtOH afforded **7e** as pale yellow plates; mp 151—152 °C; IR (Nujol) 1719, 1703 (br), 1547, 1336 cm^{-1}; ^1H NMR δ = 1.25 (3H, t, J = 7.3 Hz), 1.32 (3H, t, J = 7.3 Hz), 3.31 (3H, s), 3.58 (1H, d, J = 8.8 Hz), 4.23 (2H, q, J = 7.3 Hz), 4.35 (2H, q, J = 7.3 Hz), 4.73 (1H, dd, J = 8.8, 2.6 Hz), 5.69 (1H, d, J = 2.6 Hz), 8.51 (1H, d, J = 2.3 Hz), 8.74 (1H, d, J = 2.3 Hz).

Found: C, 44.76; H, 3.89; N, 12.11%. Calcd for $C_{17}H_{18}N_4O_{11}$: C, 44.94; H, 3.99; N, 12.33%.

Deacetylation of 3c. 4-(Ethoxycarbonyl)methyl-1-methyl-6,8-dinitro-2-quinolone (5): The 2-quinolone **3c** (50 mg, 0.13 mmol) was charged on a silica gel column (10 g) and kept for 1 d. Elution with 1 : 1 $CHCl_3$–EtOH afforded deacetylated product **5** (43 mg, 0.13 mmol) as yellow needles; mp 160—161 °C; IR (Nujol) 1716, 1682, 1531, 1346 cm^{-1}; ^1H NMR δ = 1.32 (3H, t, J = 7.3 Hz), 3.53 (3H, s), 3.95 (2H, s), 4.29 (2H, q, J = 7.3 Hz), 6.97 (1H, s), 8.84 (2H, brs).

Found: C, 49.98; H, 3.78; N, 12.49%. Calcd for $C_{14}H_{13}N_3O_7$: C, 50.15; H, 3.91; N, 12.53%.

Reaction of 3a with $MeNHNH_2$. 1-Methyl-6,8-dinitro-4-(1,3,5-trimethyl-4-pyrazolyl)-2-quinolone (6): To a solution of the 2-quinolone **3a** (70 mg, 0.20 mmol) in MeOH (7.0 mL), $MeNHNH_2$ (17 μL, 0.30 mmol) was added and the mixture was refluxed for 3 h. MeOH and excess $MeNHNH_2$ were removed under reduced pressure. It was confirmed that most of the residue was pyrazolyquinolone **6** by the ^1H NMR. Purification by column chromatography with EtOH afforded **6** (65 mg, 0.18 mmol) as yellow paste: IR (Nujol) 1674, 1537, 1346 cm^{-1}; ^1H NMR δ = 2.15 (3H, s), 2.23 (3H, s), 3.61 (3H, s), 3.94 (3H, s), 6.84 (1H, s), 8.58 (1H, d, J = 2.6 Hz), 8.85 (1H, d, J = 2.6 Hz).

Found: C, 53.96; H, 4.50; N, 19.23%. Calcd for $C_{16}H_{15}N_5O_5$: C, 53.78; H, 4.23; N, 19.60%.

Transformation of Isolated Adduct 7e into *cine*-Substituted Product 4e. To a solution of adduct **7e** (227 mg, 0.5 mmol) in EtOH (30 mL), 0.05 M NEt_3 in EtOH (15 mL, 0.75 mmol) was added at 0 °C. The mixture was warmed to room temperature with further stirring for 3 h. After concentration, the reaction mixture was dissolved into $CHCl_3$ (20 mL) and washed with H_2O (20 mL) to remove Et_3NHNO_2. The organic layer was dried over ($MgSO_4$), and concentrated to afford the *cine*-substituted product **4e** (175 mg, 0.43 mmol).

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