BASE CATALYZED REARRANGEMENT OF AZIDOQUINONES - SUBSTITUTED ACTIVE METHYLENE COMPOUNDS.

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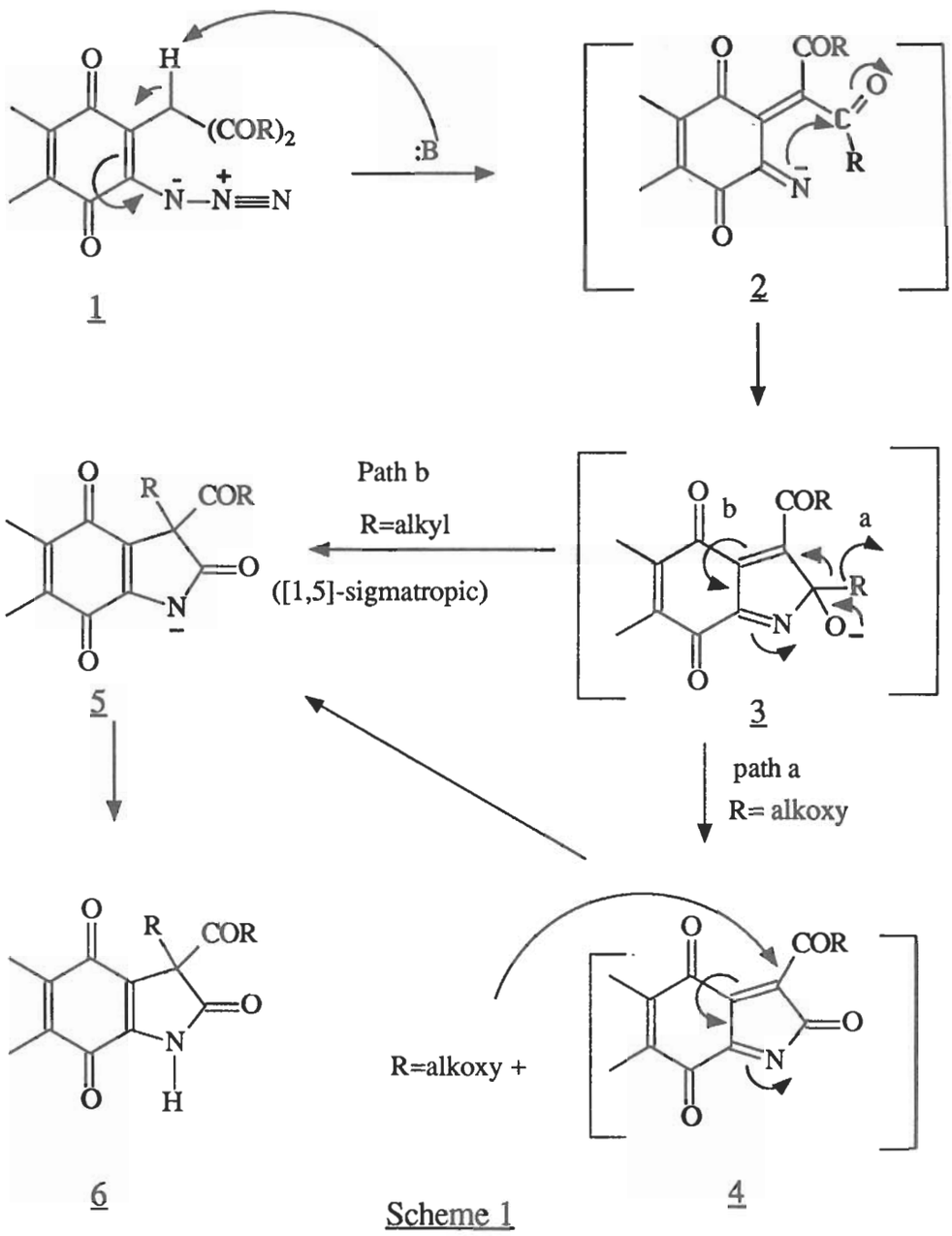
Abstract: Base catalyzed reactions of 2-azido-2,4-quinones having an active methylene group at the 3-position result in the formation of substituted 2-oxo-indole quinones. The reaction involves 1,4-elimination of N_2, followed by ring closure induced by nucleophilic attack of the resulted azadiene anion on the proximate electrophilic site. The oxy anion formed undergoes migration of an alkyl or alkoxy group to the 3-position giving the product. The mechanism of the migration is suggested to be either a concerted or an ionic process depending on the nature of the migrating group.

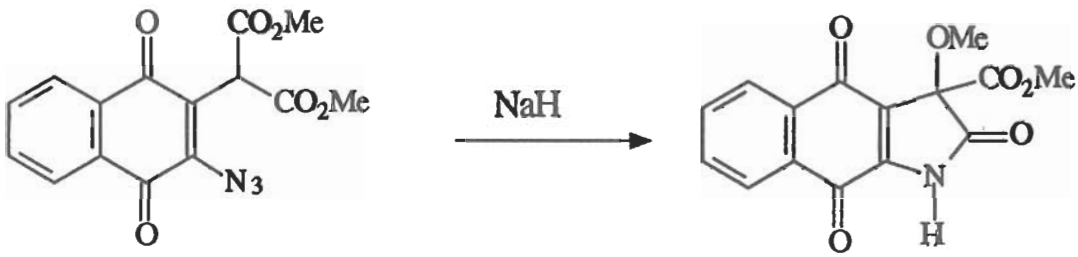
Azidoquinones substituted with active methylene compounds are referred to as 2-azido-3-[2-(1,3-dioxo)-]-1,4-quinones, 1. Recently, this class of compounds has been shown to undergo a series of transformations that involve quinone - quinone methide equilibration and led to heterocyclic quinones.[1] Presented here are new reactions of these azidoquinones, 1, that involve rearrangement of 1 to indolequinones by action of a base. These reactions provide a potential synthetic route to heterocyclic quinones.

The general reaction sequence for the rearrangement is outlined in Scheme 1. Base abstraction of the acidic proton which is on the α-carbon to the quinone nucleus, followed by elimination of N_2 by 1,4-elimination fashion.[2] The resulting azadiene anion intermediate, 2, would undergo intramolecular nucleophilic attack at the proximal electrophilic site (the carbonyl), giving 3. The heterocyclic oxyanion, 3, would be a very reactive intermediate and rearrange to give indolequinone 6 after protonation. The rearrangement follows either path a or b depending on the nature of the R group. The reaction goes by path a if R group has an ionic character, i.e. R=alkoxides. In this case, intermediate 4 would be formed by elimination of R, which then proceeds to 5 by 1,4-addition reaction. Thus, the rearrangement through path a is purely ionic. However, when R is an alkyl group, the reaction follows path b which is believed to be a concerted process by a [1,5] sigmatropic shift.

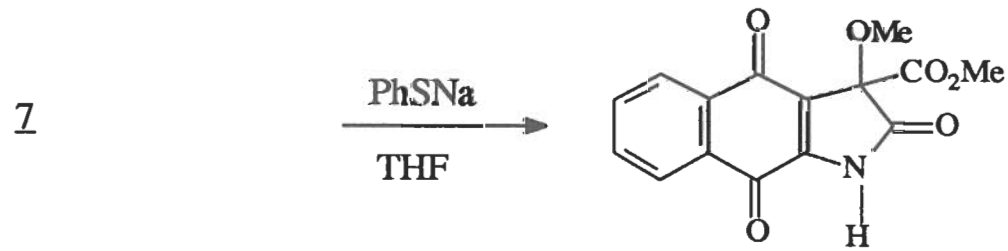


Scheme 1

The following are representative of the above reaction sequence. Slow addition of azidoquinone 7 in THF to a solution of THF containing one equivalent of NaH, produced indolequinone 8 in 70% yield. However, when the azidoquinone 7 was added to a solution of sodium phenylthiolate, the indolequinone 9 was isolated in 47% yield (Scheme II). The reactions suggest that they proceed by path a, in which an intermediate such as 4 was trapped by PhS^- rather than the CH_3O^-.



7 8 (70%)

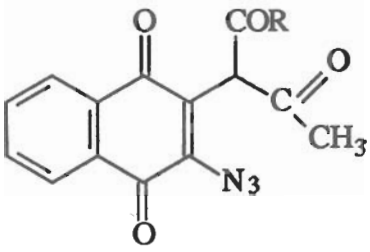


9 (47%)

Scheme II

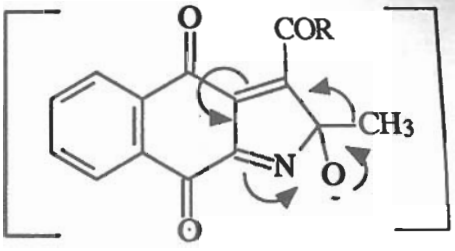
The rearrangement that goes by path b mechanism is examplified with azidoquinones 10a and 10b. These two quinones produce indolequinone 12a and 12b, in 40% and 25% yield respectively, when subjected to NaH in THF (Scheme III).

It is of particular interest to note that the facile methyl migration process represents an example of the assisted oxy [1,5] sigmatropic rearrangement.[3] The structure of these products are based upon their spectral and analytical properties. Structural data for 12a and 12b are given below. 12a: m.p.207.5-208.5 ; IR(KBr, cm^{-1}) 3250 (m), 1715 (s) 1640 (m), 1595 (m), 1550 (s); ^1H NMR ($CDCl_3$) δ 1.29 (t,3H,J=7Hz), 1.86 (s,3H), 4.26 (q,2H;J=7Hz),7.70-7.91 (m,2H), 8.08-8.29 (m,2H); ^{13}C NMR ($CDCl_3$) δ 14.17(q), 20.85(q), 63.27(t), 72.70(s), 108.12(s), 126.96 (d), 127.67(d), 131.93(s), 132.99(d), 134.72(s), 136.43(d), 165.13(s), 166.10(s), 177.14(s), 179.60(s), 192.04(s); MS (M^+), calcd for $C_{16}H_{13}NO_5$ 299.07935, found 299.08105. 12b: m.p. 187-189; IR (CH_2Cl_2,cm^{-1}) 3240(w), 1700(s), 1660(s), 1640(s) 1550(m); ^1H NMR ($CDCl_3$) δ 1.70 (s,3H), 2.16 (s,3H), 7.47-7.71 (m,2H), 8.01-8.15 (m,2H), 9.10 (broad, 1H); MS(M^+) calcd for $C_{15}H_{11}NO_4$: 269.0688, found 269.0701.



10 a,b

NaH



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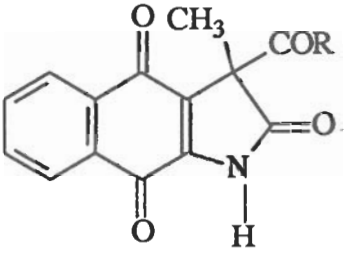

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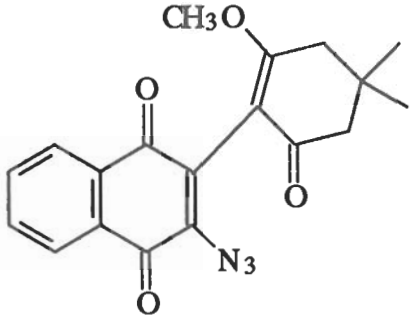
12a: R= OC_2H_5 (40%)

12b: R= CH_3 (25%)

Scheme III



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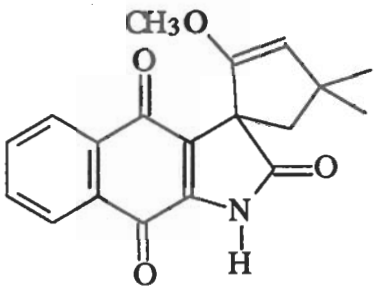
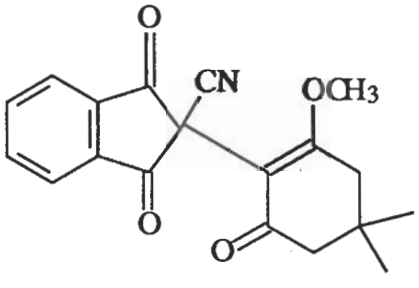


14 (35%)

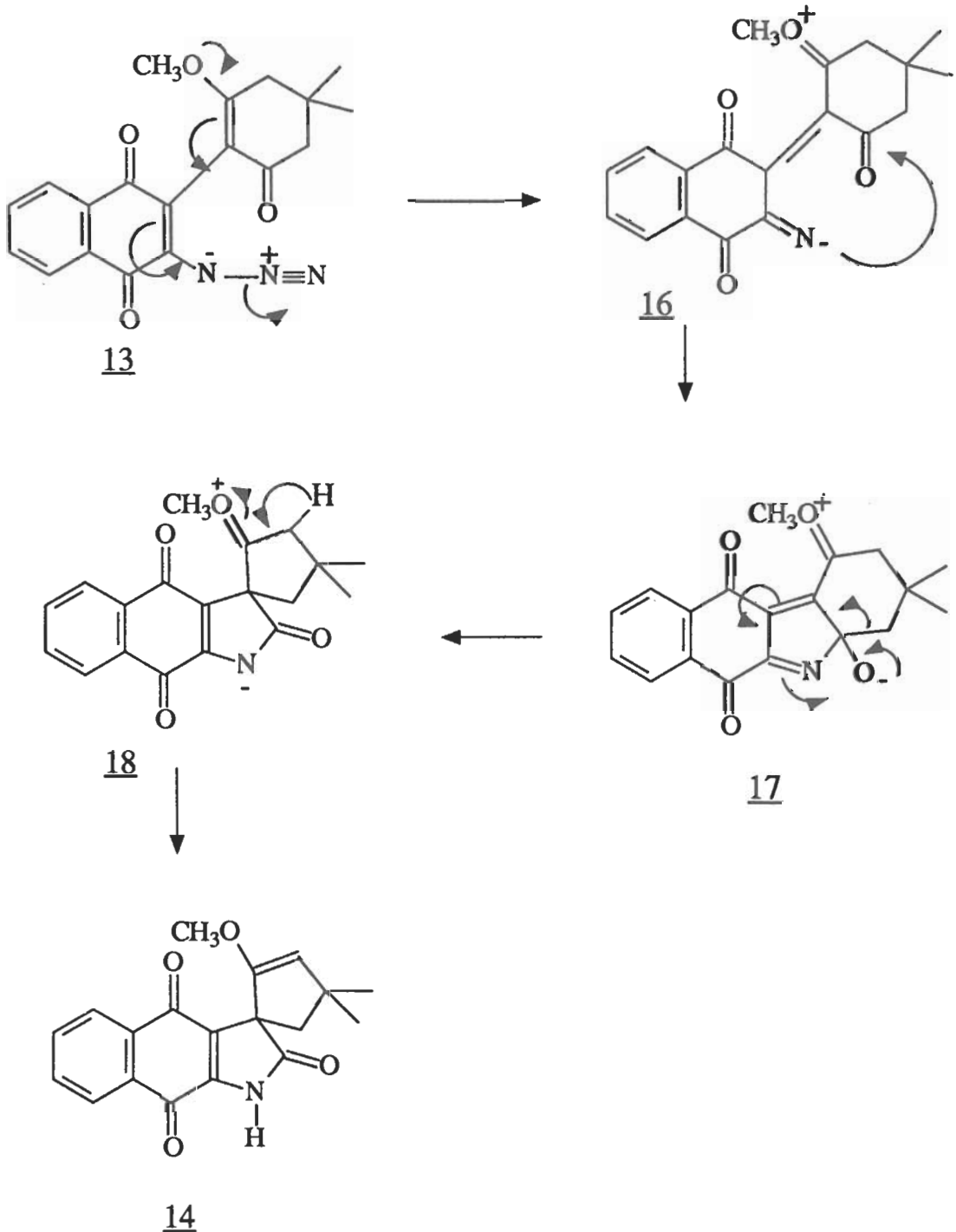
+



15 (40%)

Scheme IV

The last example described here is a closely related transformation . When azidoquinone 13 in toluene was allowed to reflux for 4 hrs , the spiro indolequinone 14 and the ring contracted product 15 were obtained in 35% and 40% yield, respectively (scheme IV). The formation of 15 follows the previously known thermal azidoquinone cleavage mechanism.[4] However, the mechanism of formation of 14 is closely related to the above mentioned mechanism (scheme I path b) and is illustrated in Scheme V.



Scheme V

The mechanism involves initial loss of N_2 assisted by the electron donating methoxy group (analogous to 1,4-elimination) to give 16. Intermediate 16 proceeds to 18 after ring closure followed by migration of the methylene group ([1,5]-sigmatropic shift). Rearrangement of 18 by proton elimination and neutralization gave the product 14: m.p. 288 -289°; IR(KBr,cm^{-1}) 3200(w), 1737(s), 1680(s), 1660(s), 1626(m), 1697(m); ^1H NMR ($CDCl_3$) δ 1.36 (s,3H), 1.40 (s,3H), 2.14 (d 1H, J=13.3 Hz), 2.40 (d, 1H, J=13.3 Hz), 3.53 (s,3H), 4.83 (s,1H), 7.60 (froad, 1H), 7.66-7.80 (m, 2H), 8.06-8.12 (m, 2H); Anal. Calcd. for $C_{19}H_{17}NO_4$: C: 70.58; H: 5.30. Found C: 70.58; H: 5.30.

It is noted that the generalized sequence of reaction in scheme I represents a very interesting transformation from a mechanistic point of view and provides a synthetic route to indolequinone. The synthetic utility and the scope of the reaction is under current investigation.

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REFERENCES

1. Moore and Hamdan J. Org. Chem., 1985, 50, 3427.
2. For review of 1,4-eliminations See, Wakselman, Nouveau. J. Chem. 1983, 7, 439.
3. The term Oxy [1,5] sigmatropic rearrangement is named analogous to oxy-cope rearrangement. Oxy [1,5] sigmatropic rearrangements are less common but some examples are known. See for example, Yousef and Ogliaruso, J. Org. Chem., 1972, 37, 2601.
4. Weyler, Pearce, and Moore, J. Am. Chem.. Soc., 1973, 95, 2603.