SUBSTITUTED 1,2,3-TRIAZOLIUM-1-YLIDES AS 1,3-DIPOLES: SYNTHONS FOR A RANGE OF AZIMINE AND 1,2,3-TRIAZA SYSTEMS

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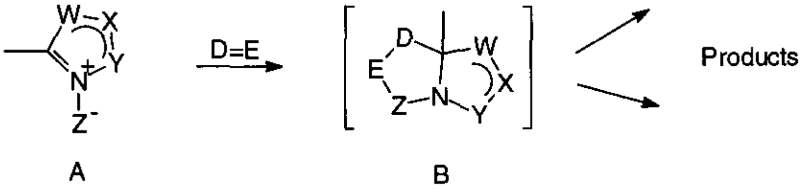
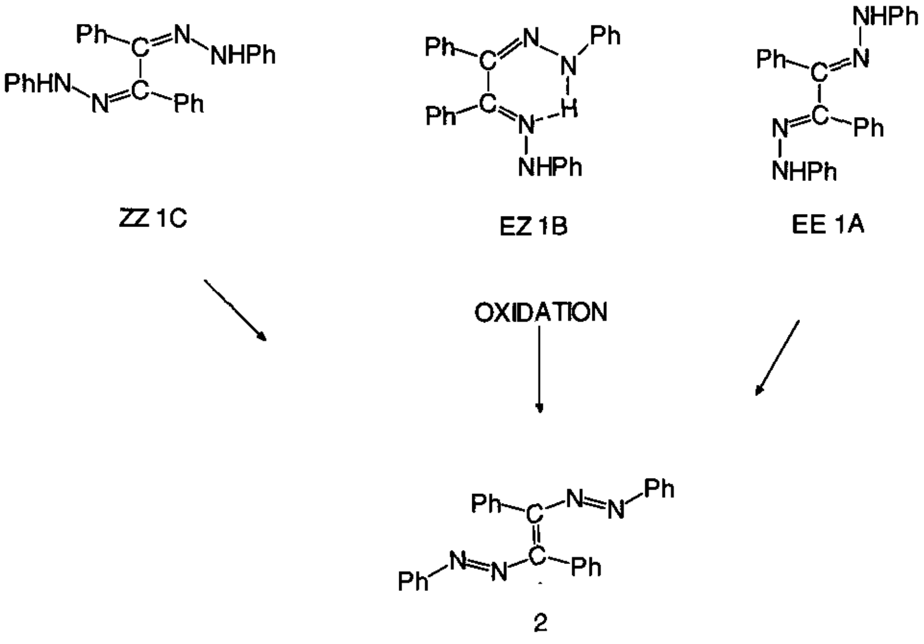
Abstract - The synthetic scope of the 1,2,3-triazolium-1-ylide system as a 1,3-dipole is outlined.

The chemical versatility of the benzo 1,2,3-triazole system has been extensively demonstrated in recent years by Katritzky.[1-3] This arises partly because the 1,2,3-triazole system can behave as both an electron sink and an electron source. Herein we wish to draw attention to another useful feature of the 1,2,3-triazole ring which arises when the ring contains a substituent at N-2. In such systems the N-N(R)-N linkage is remarkably durable and the 2-substituted 1,2,3-triazole system can be used as a synthon for many molecules containing this 1,2,3-triaza structural unit. 1,3-Dipoles where two of the four pi electrons are part of an azole ring e.g. A, are synthetically useful because the adducts B derived from them are unstable and undergo unexpected and easy rearrangements giving high yields of products. Studies on a range of such 1,3-dipole systems have been reported, involving azole rings such as pyrazole,[4] imidazole,[5-9] 1,2,4-triazole,[10] 1,2,3-triazolopyridium,[11] tetrazole,[12] 1,2,5-oxadiazole,[13,14] and thiazole[15-17].



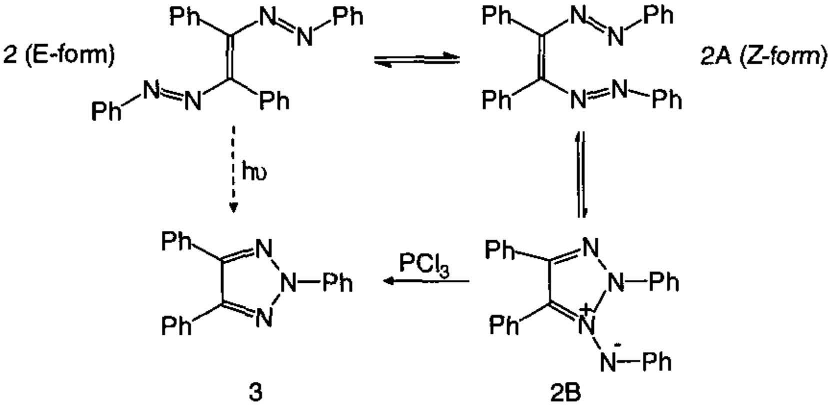
In all cases the initial 1,3-dipolar cycloadditions are followed by rearrangements which may run into a number of steps sometimes involving a second molecule of dipolarophile thereby developing into tandem reactions. This complexity was not fully appreciated in the early reports and many products have been erroneously described as the simple primary adducts. Among the range of azolium-1,3-dipole types, those based on the 1,2,3-triazole system, described herein, are to date one of the most versatile and synthetically useful.

Triazolium-1-imides: The 1,2-bisphenylhydrazone of benzil has three stable isomers, 1A, 1B, 1C (Scheme 1), discovered by Spassov[18] and investigated by Woodward.[19] Oxidation of each or any of them gives the same *trans*-azo compound (2).[19,20]



Scheme 1

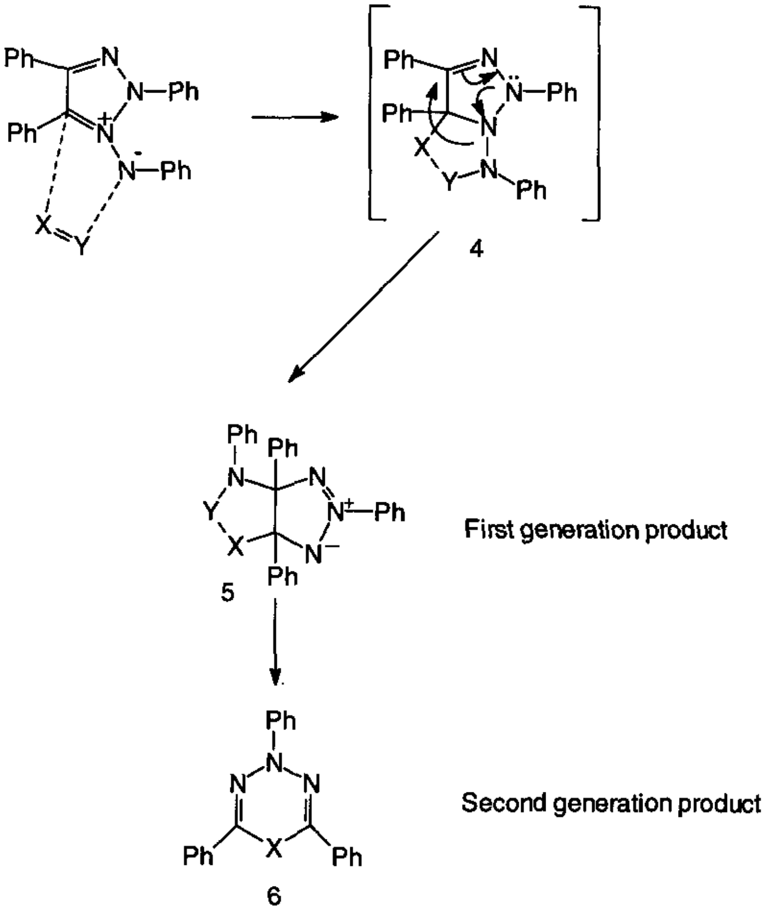
A little known X-ray structure of 2 has been reported.[21] In solution compound (2), (and a wide range of its derivatives) gives reactions through the 1,3-dipole triazolium imide form (2B) (Scheme 2). Hence the E-form of 2 undergoes a remarkably facile E-Z isomerisation in solution followed by the electrocyclisation[22] to give the 1,3-dipole (2B). The existence of this dipole form and its potential for cycloaddition was recognised by George *et al*[23] in 1971 and because of the form (2B) most workers at the time, and since, appear to view the initial oxidation product of 1 as the Z-form (2A) (Scheme 2) which it is not. Recently we have found the easily accessible[Ψ] species (2B) and its derivatives to be exciting reagents as azolium 1,3-dipoles. These systems can also be deaminated in almost quantitative yield by warming with PCl_3 to give 1,2,3-triazoles such as 3 (Scheme 2) and this is a simple route to such triazoles. Uv photolysis of 2 also gives the triazole in unspecified yield.[24]



Scheme 2

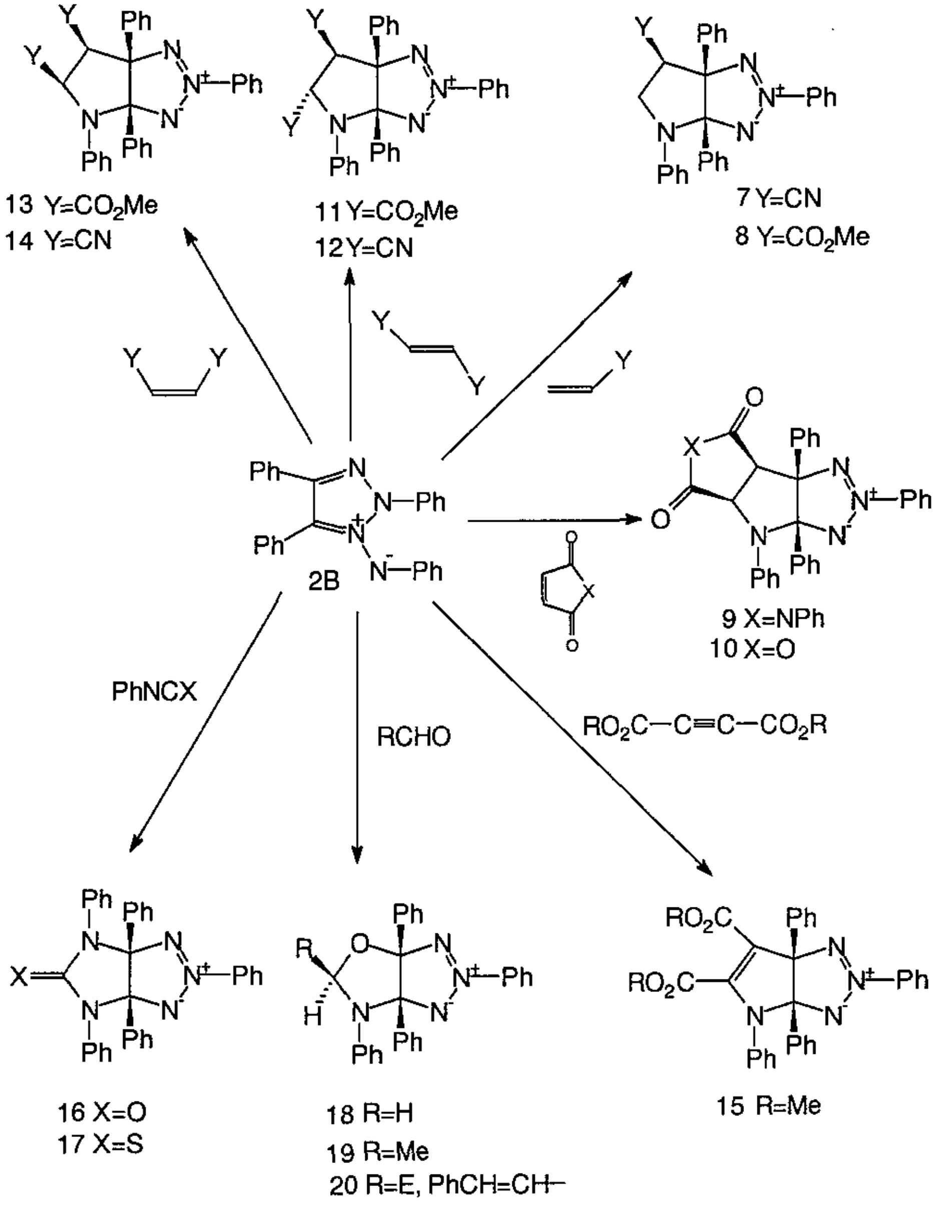
Adducts derived from the dipole (2B) have the initial structure (4) (Scheme 3). In this the N-N bond which is exocyclic to the 1,2,3-triazole moiety is labile and undergoes 1,4-electrocyclic rearrangement to give the fused structure (5) which we will refer to as a first generation product (Scheme 3). Subsequent structural changes can occur *in situ* or may be induced with the first generation product and these give rise to a second generation of products adding to the synthetic scope.

Compound (2B) is a type I 1,3-dipole (HOMO controlled reactions with most dipolarophiles)[25] and is reactive with a wide range of 2π-systems. The range of stable first generation products available from (2B) is illustrated in Scheme 4. All of these reactions are simple one-pot processes involving stirring or heating of 2 with the dipolarophile in dry solvents such as acetone, methyl ethyl ketone or toluene.



Scheme 3

Thus with monosubstituted ethenes products such as 7 and 8 (Y exo) are formed from an initial endo cycloaddition followed by rearrangement (Schemes 3 and 4).[26] With 1,2-disubstituted ethenes the reaction is rigidly stereoselective and regioselective[26] giving single products, examples of which are compounds (9-14). While the regioselectivity holds with trans 1,2-disubstituted ethenes for compound (2B) itself, with some different derivatives of 2B it does not necessarily hold and mixtures of trans-isomers of 11 and 12 have been



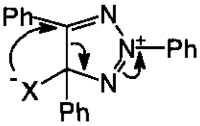
Stable First Generation Products

Scheme 4

encountered, for example when the bridgehead phenyl groups were replaced by $(CH_2)_4$. The stereoselectivity was retained in all cases. Treatment of 2B with acetylenedicarboxylates[26] gives fused pyrrolidinotriazolines such as 15 and with phenylisocyanates and isothiocyanates[27] the fused imidazolotriazoline products (16) and (17) are formed. In cycloaddition reactions, with aldehydes the first generation products are the fused oxazolotriazolines (18-20) in which the substituent R is again exo from an initial endo cycloaddition.[28,29] Most of these products are new fused bicyclic systems. They all arise by the route shown in Scheme 3 involving a cycloaddition followed by an *in situ* 1,4-N→C sigmatropic rearrangement.

With some dipolarophiles the first generation products are not stable and they progress *in situ* to stable second generation products (Scheme 5).

Thus treatment of compound 2B with N-sulphinyl aniline[29,30] gives the tetrazine (21) and treatment of 2B with methyl cyanodithioformate[29,31] gives the sulphur analogue of this, 22 . In these products a ring expansion of the triazole 4,5-bond in (2B) has occurred through a fragmentation of the unstable first generation product (5). A similar process can be induced by heating the stable first generation products (15) to give 24 and either of 18 , 19 , or 20 to give the oxygen analogue (23)[29,32]. The systems (21-23) are interesting 8π-6-atom rings which if planar would be anti-aromatic. The molecules are boat shaped[31] with substituents arranged axially or equatorially so that lone-pairs on adjacent atoms lie in approximately orthogonal orientations. Compounds of type (24) (CN for CO_2Me) can also be obtained by dehydrogenation of 12 or 14 in a reaction which proceeds via an intermediate of type (15), (CN for CO_2Me).[32] While the mechanism of these ring expansions is still under investigation the pathway is likely to involve an intermediate of type (25) or (26).



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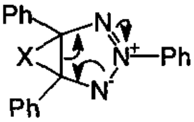

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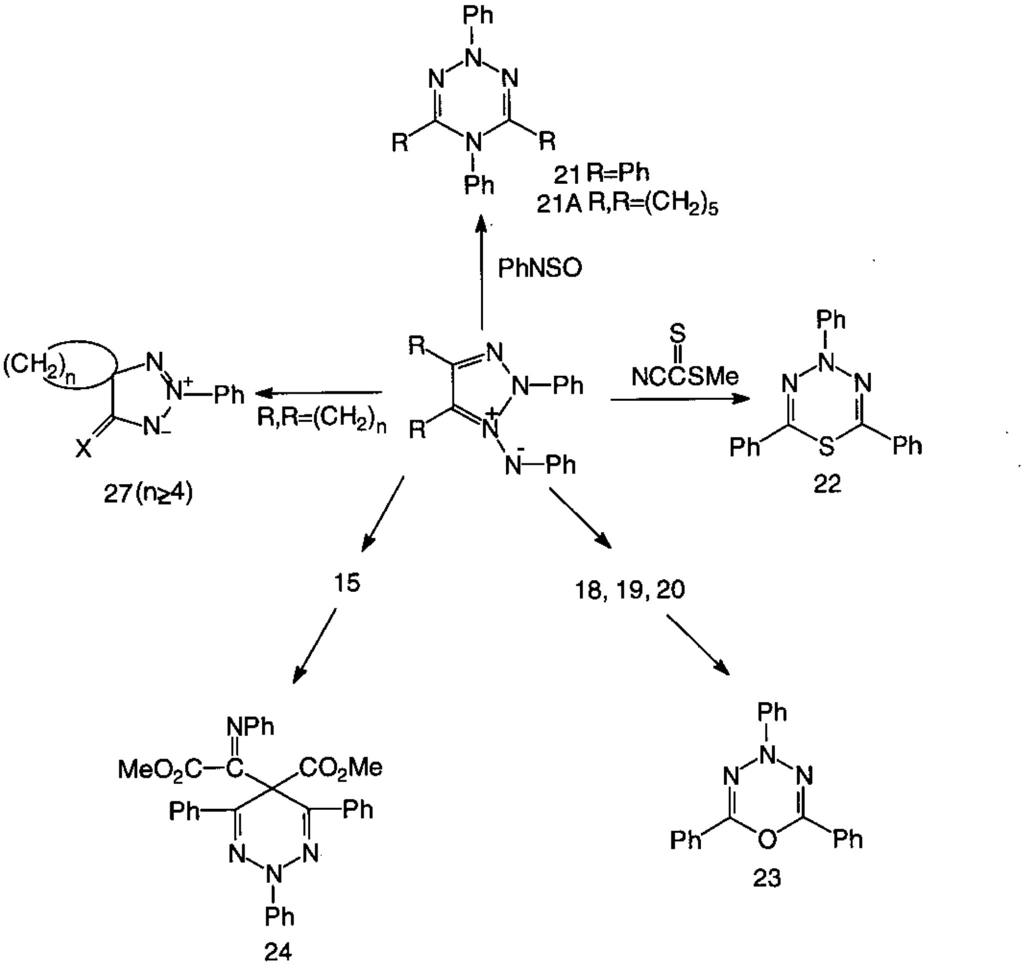
We have recently found that the compounds (22) can also be obtained from the dipoles (2B) by simple treatment with dry H_2S in an interesting reaction which must lend support for a species of type (25) (X=S).



Stable Second Generation Products

Scheme 5

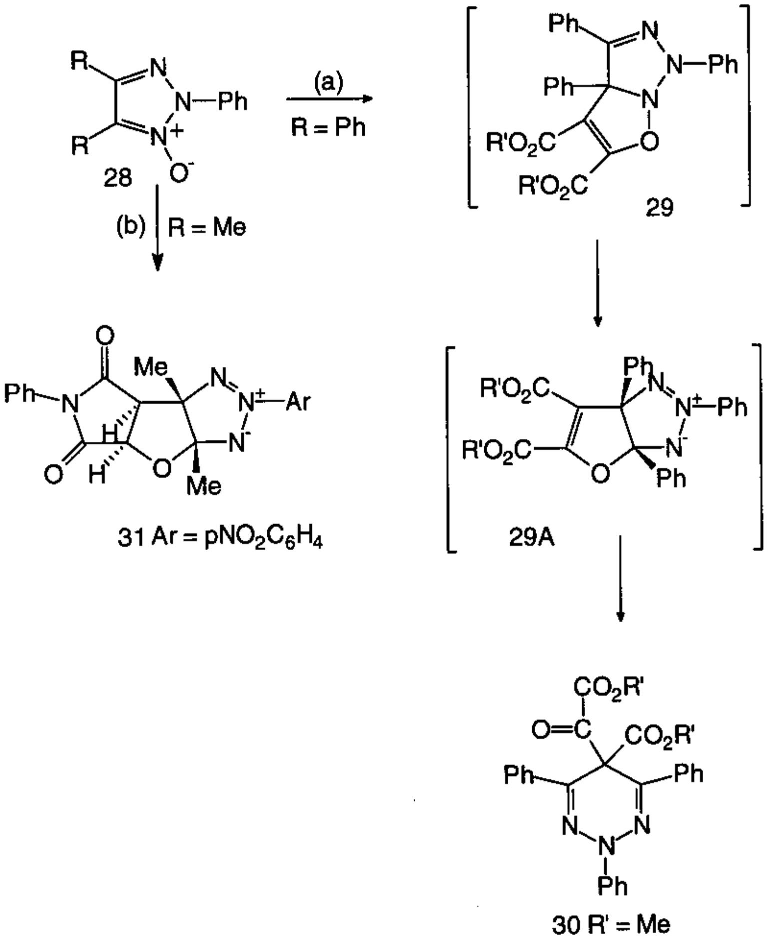
An interesting variation of these reactions occurs when the 4,5-phenyl groups of 2B are replaced by a methylene chain. For $[CH_2]_5$ compound (21A) is obtained from PhNSO but for $[CH_2]_4$, the methylene chain is too short for a bridging link between the two tetrazine carbons in structures (21A) and a 1,2-shift occurs on the triazole 4,5-bond giving a ring contraction and entry to the spirotriazoline series (27) (X=NPh). This entry is extended further through the formaldehyde derived products (18), $(CH_2)_n$ for Ph, which on heating with HOAc give the spiro products (27) (X=O) for n = 5 and 6 as well as 4.

All of the reactions described worked equally well for normal substituents in the phenyl ring of compound (2) or any of the dipolarophiles. All of this chemistry can be halted by structurally inhibiting the electrocyclisation (2A→2B). Thus in 1,2-bisarylazocyclobutenes and 1,2-bisarylazocyclopentenes ring strain prevents the electrocyclisation and none of these reactions are observed.[33] For these fused 1,2,3-triazolo-cycloalkene systems the 1,3-dipole chemistry begins at six carbons for the cycloalkene and we have carried it through to eight carbon rings to date.

Triazolium-1-Oxide and 1-Methanides:

Triazolium-1-oxides (28), prepared by the oxidation of benzil mono-oxime monophenylhydrazone, are much less reactive than the imides as 1,3-dipoles and they show no reactions with most of the dipolarophiles mentioned.[34] However with strongly π deficient systems such as acetylenedicarboxylates and N-substituted maleimides they give useful reactions which parallel those already described[34](Scheme 6).

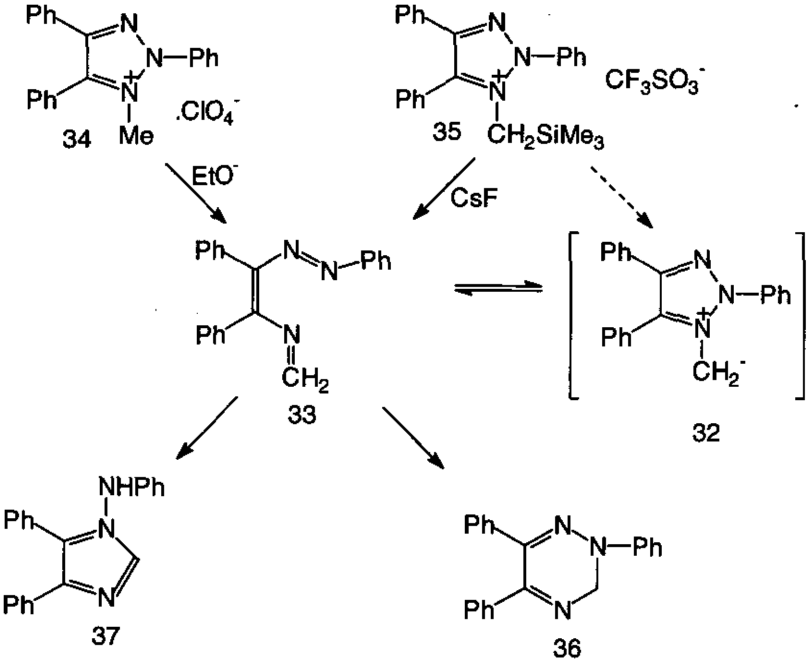
Thus heating of the dipoles (28) with dialkyl acetylenedicarboxylates in toluene gives the products (30) which arise via the unstable precusors (29) and (29A) the latter of which is the oxygen analogue of the stable products (15). Products of type (31) were also obtained from the reaction of the dipoles (28) with substituted N-phenylmaleimides but the range of derivatives was somewhat limited.[34] These products are expected since the N-O bond in the initial adduct (29) should be more labile than the corresponding N-N bond in the adducts (4). Hence for the N-oxides (28) the synthetic limitations arise from the lower energy HOMO of the dipole which makes it unreactive with normal dipolarophiles.



Reagents (a) $R'O_2C-C\equiv C-CO_2R'$
(b) N-phenylmaleimide

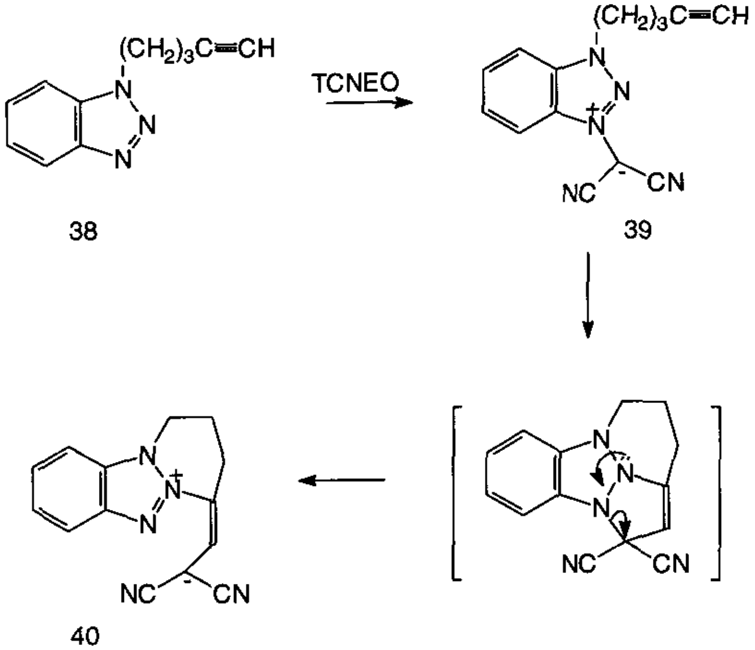
Scheme 6

Ab inito calculations suggest that the equilibrium between the 1,2,3-triazolium-1-methanide dipole (32) and the acyclic 1,2,5-triazatriene isomer (33) should lie strongly in favour of the latter with relatively small activation barrier between them.[35] Attempts to generate the dipole (32) by treatment of the triazolium salts (34) and (35) with base (Scheme 7) resulted in successful removal of H^+ and $^+SiMe_3$ from the alkyl groups but the products were the compounds (36) and (37) from the acyclic species (33) and initial attempts to intercept the dipole (32) with added dipolarophiles failed. Recently we have found that the Me_3Si group of 35 can be removed in the absence of base and that the dipole (32) may be present under these conditions for a short time. We hope to report further on this in the near future.



Scheme 7

Triazolium-1-methanides with electron withdrawing groups on the methanide carbon should be more stable. The dicyanomethanide group,-$C^-(CN)_2$, has been used in a number of imidazolium and azinium or pyridinium methanide 1,3-dipole systems.[36-38] It is inserted by treating the heterocycle with tetracyanoethylene oxide (TCNEO). However the 2-substituted 1,2,3-triazole system is not nucleophilic enough to react with TCNEO.[39] However 1-alkylbenzo-1,2,3-triazole can extract the dicyanomethanide group from TCNEO[39] and the dipole (39) has recently been prepared from the N-alkylbenzotriazole (38).[40] This benzo-1,2,3-triazolium-1-dicyanomethanide 1,3-dipole (39) possesses an internal alkyne dipolarophile and on being heated it cyclised to the product (40) (Scheme 8).[40]



Scheme 8

Conclusion and Prospect:

The synthetic scope of the 1,2,3-triazolium-1-ylide system has been outlined. At present this resides mainly in the 1-imide derivatives of which 2*B* is the parent phenyl *substituted* compound. The ease of synthesis[Ψ] of 2B makes this a useful synthetic reagent in its own right as a synthon for molecules containing the 2-substituted 1,2,3-triaza moiety. The 1,2,3-triazole case is but one example of a much wider heterocyclic synthetic domain based on the use of exocyclic azolium ylides of type (A) as azolium 1,3-dipoles. The outline of the first two *steps in a general sequence* is visible in the behaviour of the 1,2,3-triazole system, namely a cycloaddition followed by a first rearrangement involving cleavage of the weakest bond (often N-N or N-O) in the adduct and its replacement by a stronger bond. Further rearrangements, fragmentations or cycloadditions may then follow.We hope this work will help to bring about a renewal of interest in this approach to heterocyclic synthesis.

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[Ψ] When a solution of benzil (10 g, 0.048 mol) and phenylhydrazine (9.4 ml, 0.096 mol) in methanol (100 ml) containing glacial acetic acid (15 ml) was stirred under reflux for 2 h compound (1A), (98%), separated, mp 234° C (from EtOH).

Oxidation of 1A , (alternative procedures)

(1) A suspension of 1A (1 g, 2.56 mmol) in dichloromethane (25 ml) was treated with lead dioxide (0.73 g, 3.07 mmol) and stirred for 18 h at ambient temperature. Insoluble salts were removed, and washed thoroughly with dichloromethane. Evaporation of the combined mother-liquor and washings gave 2 , mp 178-179°C (from benzene-petroleum spirit bp 60-80° C)(80%).

(2) A suspension of 1A (1 g, 2.56 mmol) in anhydrous Et_2O (15 ml) and a solution of I_2 (2 g, 7.88 mmol) in anhydrous Et_2O (20 ml). The mixture was stirred at room temperature for 3 h. The resulting precipitate was filtered, washed with petroleum spirit, suspended in water and dried to give a red brown solid (2) mp 178-179° C(from benzene-petroleum spirit bp 60-80° C) (85%).

(3) A suspension of 1A (1 g, 2.56 mmol) in glacial acid (20 ml) was treated with lead tetra-acetate (1.2 g, 2.7 mmol) and stirred at room temperature for 10 min. The lead salts were decanted off and the remaining precipitate filtered and washed with petroleum spirit, to give a red brown solid mp 178-179° C (from benzene-petroleum spirit bp 60-80°) (80%).

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