Dual Synthesis of 1*H*-[1,2,4]Triazolo[3,4-*a*]isoindoles and New 1*H*-[1,2,4]Triazolo[5,1-*a*]isoindoles − Experimental and Theoretical Approaches

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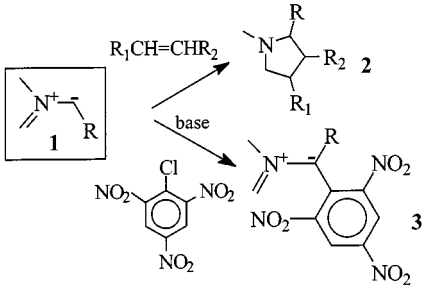
The syntheses and characterization of 4-substituted 4*H*-[1,2,4]triazol-1-ium phenylmethylides **8c–e** and the new 5-aryl-1-phenacyl-1*H*-[1,2,4]triazolo[5,1-*a*]isoindole core **13** are reported for the first time. Treatment of triazolium salts **6c–e** with triethylamine in the presence of picryl chloride resulted in a regioselective mixture of disubstituted ylides **7c–e** and **8c–e**. Intramolecular annulation of the latter in DMSO resulted in the formation of 1*H*-[1,2,4]triazolo[3,4-*a*]isoindole and 1*H*-[1,2,4]triazolo[5,1-*a*]isoindole derivatives, respectively . In order to explain this unusual chemical behavior, a theoretical approach, using AM1 and PM3 procedure methods, is also presented.

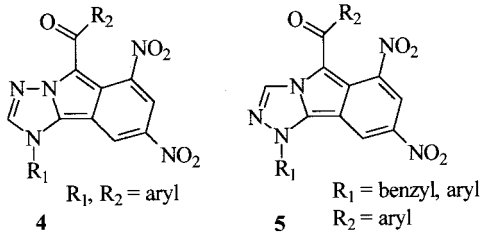
Introduction

The synthetic utility of heterocyclic mesomeric betaine **1** is widely recognized[1−3] For example, it is well known that the monosubstituted ylide **1** is able to take part in 1,3-dipolar cycloadditions with a large variety of dipolarophile compounds, which is a traditional way to form five-membered fused heterocycles **2** (Scheme 1). The reaction of this class of compounds with strong electrophiles such as picryl chloride[4−11] has also been described and used in particular to trap the reactive species **1**.



Scheme 1. Reactivity of the monosubstituted ylides

As a part of our research program on the reactivity of disubstituted ylides **3** and their application in the synthesis of aza-fused heterocycles, we have recently reported the synthesis of 4-subsituted 4*H*-[1,2,4]triazol-1-ium[12] and 1 substituted-1*H*-[1,2,4]triazol-4-ium 2,4,6-trinitrophenylmethylide[13] derivatives. These species underwent intramolecular annulation in moderate to good yields to form the 1*H*-[1,2,4]-triazolo[5,1-*a*]isoindole (**4**) and 1*H*-[1,2,4]-triazolo[3,4-*a*]isoindole (**5**) derivatives, respectively.



This procedure provided a good method for preparation of these unusual frameworks. However, when this experiment was carried out with different substitution patterns (**6c−e**) with R_2 = Br, OCH_3 and NO_2 in the 1,2,4-triazole series, the course of the reaction changed slightly. Surprisingly, two isomeric forms of disubstituted ylides **7** and **8** were detected (Scheme 2).

Thus, in the light of the experimental findings described above, it was possible to envisage two concomitant ways by which isomeric isoindole cores might be synthesized. In this paper, the synthesis of triazolium salts **6c−e** and their chemical behavior under basic conditions are reported. The synthesis of triazol-1-ium phenylmethylides **8c−e** and 1-substituted 5-aryl-1*H*-[1,2,4]triazolo[5,1-*a*]isoindoles is also described for the first time. Additionally, in order to explain the observed regioselectivities, a theoretical approach using AM1 and PM3 calculations is reported.

Results and Discussion

The required salts **6c−e** were easily prepared in two steps from the available 1*H*-[1,2,4]triazole **9** (Scheme 3). Treatment of 1*H*-[1,2,4]triazole **9** with sodium in ethanol, followed by the addition of benzyl bromide, produced a separable 90:10 mixture of 1-benzyl[1,2,4]triazole and 1-benzyl-[1,3,4]triazole.[14] The 1-benzyl[1,2,4]triazole derivative **10**

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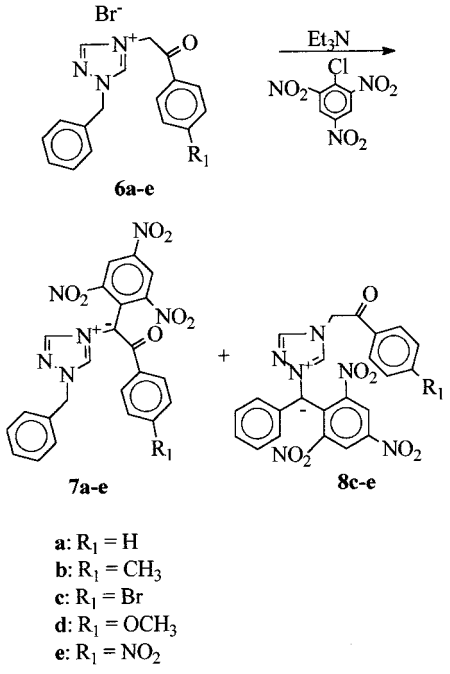
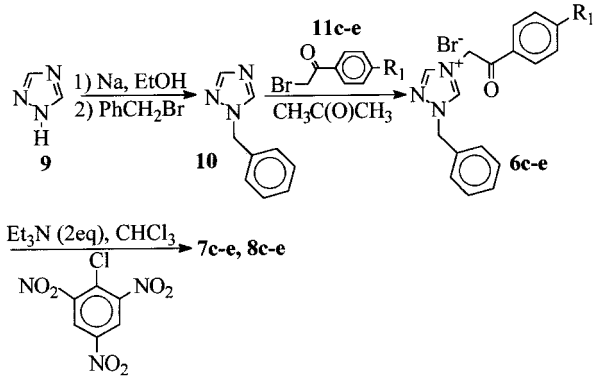


Scheme 2. Reaction between the 1,2,4-triazolium salts and picryl chloride

was then treated with commercial 4-substituted 2-bromoacetophenones **11c−e** to produce the corresponding 1-benzyl-2-(4-substituted phenacyl)[1,2,4]triazolium bromides **6c−e** exclusively. This synthesis is also known as the "salt method".[15,16]



Scheme 3. Preparation of the disubstituted ylides

All quaternized products were characterized by ^1H and ^{13}C NMR spectroscopy. In all cases, N^1-CH_2Ph and $^+N^4-CH_2C(O)$ signals were observed as a singlet in the chemical shift range from $\delta = 4.5$ to 6.13, while ^{13}C NMR spectra showed the C=O resonance at $\delta \approx 188$.

When the unsymmetrical triazolium salts **6c−e**, dissolved in chloroform at room temperature, were treated with triethylamine (2 equiv.) as base in the presence of picryl chloride, a mixture of two isomeric ylides **7c−e** and **8c−e** was obtained. Experimentally, in order to avoid the decomposition of the ylides by cleavage of the N^+-C^- bond, all ylide syntheses were performed in the absence of light. Disappointingly, all attempts to isolate isomers **7** and **8** failed. Nevertheless, the structure assignments of the disubstituted ylides **6** and **7** were unambiguously established by ^1H NMR spectroscopy of the crude product. The ^1H NMR spectroscopic data clearly indicate the disappearance of one methylene group in each isomer compound and the presence of two downfield singlets, appearing at $\delta \approx 8.6$, corresponding to the two magnetically equivalent CH units in the nitroaromatic moiety.

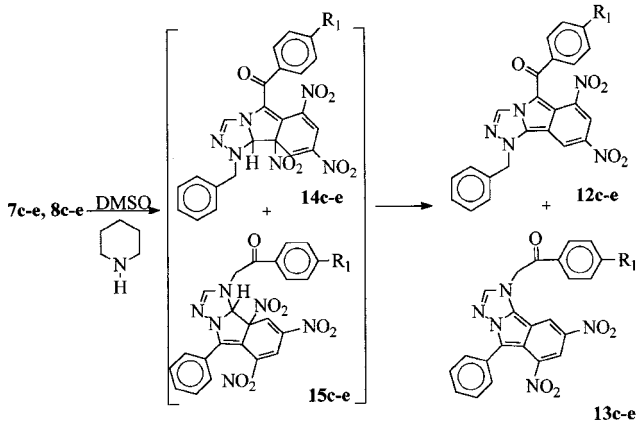
In the mass spectra, moreover, a unique molecular peak was detected in each mixture of disubstituted ylides. The ratios of the N^1 and N^4 isomer ylides in the isomeric mixtures were estimated from the relative intensities of the remaining methylenic protons. The data are reported in Table 1.

Table 1. Salts **6c−e**, disubstituted ylides **7c−e** and **8c−e** and isoindole derivatives **12c−e** and **13c-e**

Compound	Yield [%]	Ratio[a] of crude mixture **7/8** [%]
6c	76	–
6d	47	–
6e	75	–
7c, **8c**	80	72:28
7d, **8d**	61	73:27
7e, **8e**	78	87:13
12c	76	–
12d	68	–
12e	54	–
13c	82	–
13d	78	–
13e	67	–

[a] Isomer ratio based on ^1H NMR analysis of product mixture.

Next, each mixture of ylides **7** and **8** was dissolved in dimethyl sulfoxide (DMSO) and treated with piperidine at room temperature to afford, as expected, a mixture of the cycloadducts **12c−e** and **13c−e**. Every compound of type **12c−e** and **13c−e** was separated by flash chromatography (Scheme 4).



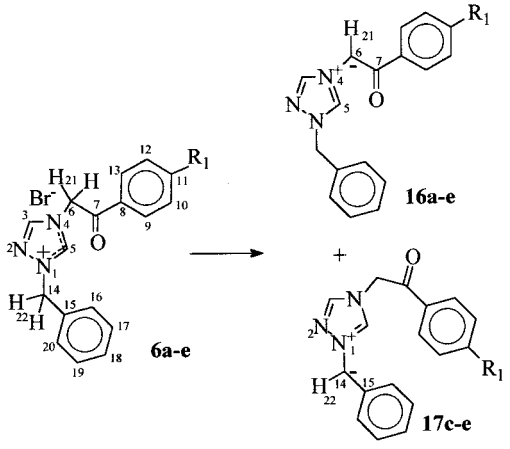
Scheme 4. Isoindole derivatives

In the intramolecular condensation of species **7** and **8**, the primary cycloadducts **14c−e** and **15c−e** were not usually isolable, because nitrous acid was easily eliminated, giving the corresponding, highly conjugated products **12c−e** and **13c−e**. The structures of compounds **12c−e** and **13c−e** were supported by NMR spectroscopic (^1H, ^{13}C), and CHN elemental analysis. The signals of the methylene pro-

tons of compounds **12** and **13** appeared in the region δ = 5.82−6.10 (and 9.20−9.70 for the remaining proton in the triazole ring) and, in the ^{13}C NMR spectra the corresponding methylene carbon resonated in the region δ = 49−54 (and between δ = 182.4 and 180.2 for the C=O group) . Nevertheless, there were no large chemical shift differences between compounds **12** and **13**. Thus, in order to confirm the assignment of the signals of each compound, we developed a GATEDEC[17,18] sequence. The result of this experiment clearly showed a singlet and a triplet (J = 4.2 Hz) for the C=O group, and these were attributed to **12** and **13,** respectively.

Theoretical Study

As regards the chemical mechanism of the synthesis of the isoindole derivatives **12c−e** and **13c−e**, only the formation of two tautomeric or isomeric ylides **16c−e** and **17c−e** as intermediate products can explain this conversion (Scheme 5).



Scheme 5. Reactivity of the triazolium salts

Thus, from a theoretical point of view, in order to explain the regioselectivity observed, it is very important to estimate the difference in mobilities of the corresponding two types of protons; that is, those bonded to C6 and C14 in salts **6a−e**. Afterwards, each monosubstituted triazolium ylide can react independently with picryl chloride to form the corresponding disubstituted triazolium ylides **6c−e** and **7c−e**. This was the reason for extending our theoretical study on the reactivity of the two types of ylidic carbon atoms C6 and C14.

Materials and Methods

Our study was based on molecular mechanics, the MM3 and semiemperical, AM1[19] and PM3[20−22] procedure methods, using Cache on a Power PC 9600/200 and a PC Computer. In this paper, we focused on the 1,2,4-triazolium salts **6a−e** and the corresponding monosubstituted 1,2,4-triazol-1-ium ylides **16a−e** and **17a−e.**

Firstly, all structures were subjected to geometry optimization by the MM3[23] method. Then, in order to find the most stable conformer, a multi-pass sequential search, involving all five single bonds in the backbone, was developed. The energy minimization techniques employed were (i) the steepest descent for the initial minimization and for the relaxation of the starting geometry (maximum 300 steps), (ii) the conjugate gradient technique for the final refined minimization. Each structure was optimized until the energy change was less than 0.001 kcal/mol. The rotational increment was 15°. Finally, every most stable conformer obtained by the MM3 method was subjected to a new geometry optimization by AM1 and PM3 procedures. The selection of the most stable conformer was performed by ΔH (heat of formation, kcal/mol) in MM3 and by ET (Total Energy) in the AM1 and PM3 procedure methods. The numerical data in the AM1 and PM3 methods were recorded by single point calculations.

Theoretical Results

Table 2 lists some representative geometrical data of the monosubstituted triazolium ylides **16a−e** and **17a−e**, obtained by the AM1 and PM3 methods. Triazolium salts are normally considered as flexible molecules as regards the single bonds in the backbone.

In every pair of tautomeric ylides, the calculated ylide bond N^+-C^-, calculated by either of the AM1 and PM3 methods, is longer for **16** than for **17**. Taking into account the values of valence carbon atoms C6 and C14 (N4−C6−C7, N4−C6−H21 and H21−C6−C7 in ylides **16** and N1−C14−C15, N1−C14−H22 and H22−C14−C15 in ylides **17**), we may suppose that the configuration of all the ylidic carbon atoms is close to an sp^2 hybridization. The values of the dihedral angles N4−C6−C7−C8 in ylides **16** and N2−N1−C14−C15 in ylides **17** suggest a planar structure for the triazolium ring and the carbanion as the most stable conformer. Indeed, this theoretical result is in a good agreement with other previously published data[24] concerning the structure of monosubstituted cycloimmonium ylides.

The atomic charges of the hydrogen atoms in both methylenic groups of the salts **6a−e** are depicted in Table 3. In fact, no significant difference in the charges calculated by the same method could be observed. From the theoretical point of view, this would mean that the two tautomeric ylides **16** and **17** should be obtained with the same degree of probability. At first sight, such a result may appear extremely surprising, taking the nature of the two methylenic groups into consideration: One is a benzylic type, while the other is bonded to a benzoyl group. On the other hand, the presence of a second nitrogen atom in position β to the benzylic methylene group may be considered as a good explanation of this theoretical result. This is why a theoretical treatment of the monosubstituted triazolium ylides **16** and **17** may produce some supplementary knowledge on the reactivity of these molecular systems.

The values of the total energies given in Table 4 show that, thermodynamically, the formation of the phenacylylides **16** is preferred over that of the corresponding benzylylides **17**. The reaction of ylides **16** or **17** with picryl chloride

Table 2. Structural data of the most stable conformers of ylides **16** and **17**

Ylide	Method	Distance[a]	Bond angles[b]				Dihedral angles[b]	
		N^+-C^-	N4−C6−C7	N4−C6−H21	N1−C14−H15	N1−C14−H22	N2−N1−C4−C5	C5−N4−C6−C7
16a	AM1	1.358	122.02	115.91	–	–	–	−0.97
	PM3	1.362	123.16	117.25	–	–	–	−0.38
16b	AM1	1.359	122.11	115.72	–	–	–	0.47
	PM3	1.361	123.08	117.54	–	–	–	0.45
16c	AM1	1.362	122.31	115.68	–	–	–	0.04
	PM3	1.360	123.24	117.20	–	–	–	3.82
16d	AM1	1.360	122.28	116.45	–	–	–	2.19
	PM3	1.360	123.02	117.33	–	–	–	−0.79
16e	AM1	1.363	122.06	115.66	–	–	–	1.02
	PM3	1.365	122.84	117.23	–	–	–	−3.80
17a	AM1	1.347	–	–	126.02	116.38	175.91	–
	PM3	1.331	–	–	123.89	118.62	178.96	–
17b	AM1	1.347	–	–	123.76	117.18	176.83	–
	PM3	1.335	–	–	122.42	119.67	178.27	–
17c	AM1	1.348	–	–	126.17	116.39	175.89	–
	PM3	1.334	–	–	123.61	118.73	178.40	–
17d	AM1	1.347	–	–	125.70	116.50	175.41	–
	PM3	1.335	–	–	123.71	118.69	177.51	–
17e	AM1	1.334	–	–	124.13	117.49	176.94	–
	PM3	1.333	–	–	121.66	119.81	178.49	–

[a] Distances are expressed in Å. – [b] Angles are expressed in °.

Table 3. The Mulliken atomic charge of hydrogen atoms in methylene groups of salts **6a−e**

Salt	Method	Charge [ua]	
		H21	H22
6a	AM1	0.160	0.166
	PM3	0.121	0.120
6b	AM1	0.163	0.167
	PM3	0.123	0.122
6c	AM1	0.163	0.167
	PM3	0.122	0.122
6d	AM1	0.163	0.166
	PM3	0.122	0.121
6e	AM1	0.169	0.169
	PM3	0.125	0.123

Table 4. Total energy and dipole values of ylides **16** and **17**; atomic orbital coefficient and net atomic charge of C6 (**16a−e**) and C14 (**17a−e**)

Ylide	Method	*ET* [eV]	HOMO (Pz)	Charge [ua]	Dipole [D]
16a	AM1	−3319.57	−0.730	−0.46	4.35
	PM3	−3022.53	+0.720	−0.73	3.77
17a	AM1	−3318.90	+0.630	−0.31	4.33
	PM3	−3022.17	+0.616	−0.53	4.43
16b	AM1	−3475.40	+0.734	−0.46	3.99
	PM3	−3172.20	−0.721	−0.73	3.37
17b	AM1	−3473.80	+0.640	−0.31	5.14
	PM3	−3171.90	+0.628	−0.54	5.30
16c	AM1	−3659.20	−0.740	−0.46	6.07
	PM3	−3360.60	+0.721	−0.73	5.19
17c	AM1	−3658.50	−0.625	−0.30	4.11
	PM3	−3360.10	−0.618	−0.53	4.37
16d	AM1	−3795.40	+0.734	−0.46	3.75
	PM3	−3465.40	−0.721	−0.73	3.25
17d	AM1	−3794.80	+0.628	−0.31	5.28
	PM3	−4149.70	−0.618	−0.53	5.33
16e	AM1	−4150.50	−0.739	−0.46	10.41
	PM3	−3753.90	+0.726	−0.73	9.82
17e	AM1	−4149.70	−0.637	−0.30	4.72
	PM3	−3753.40	+0.628	−0.52	4.99

could be considered as a donor (ylide)−acceptor (picryl chloride) interaction. Moreover, the total atomic charges and the absolute atomic coefficient values of the HOMO of ylidic carbon atoms C6 and C14 point to the phenacylylides (N^+-C6^-) as the more reactive species (see data in Table 4).

Indeed, in all the experiments, the disubstituted triazolium ylides **7** were obtained in larger quantities than the ylides **8**. Experimentally, two disubstituted triazolium ylides **6** and **7** have been characterized only in the cases when R = Br, OCH_3, and NO_2.

Conclusion

In this paper we have described the interesting chemical behavior of salts **6c−e** under basic conditions. After quenching with picric chloride, these furnished an unexpected mixture of disubstituted ylides: phenacylylides **7** and benzylylides **8**. These disubstituted carbanion ylides **7** and **8** were then converted into the corresponding triazoloisoindole derivatives **12** and **13** in DMSO. To the best of our knowledge, the synthesis of 4-substituted-4*H*-[1,2,4]triazol-1-ium phenylmethylides **8c−e** and of the 5-aryl-1-benzyl-1*H*-[1,2,4]triazolo[5,1-*a*]isoindole core **13** is announced for the first time in this paper.

Furthermore, the presence of these disubstituted carbanion ylides **7** and **8** must unambiguously involve the formation of the corresponding monosubstituted ylides **16** and **17** as intermediates. If we take the experimental data and the theoretical results (charges, net atomic coefficient) into consideration together, we can explain the formation and the ratios of the two disubstituted ylides when R = Br, OCH_3 and NO_2. However, no simple explanation could be given for the lack of benzylylide derivatives **8a** and **8b** when R= H and CH_3. In theory, the site of deprotonation can

be estimated by quantum chemical calculation. Moreover, the presence of the solvent can interfere with and affect (i) the geometry of the salts, and (ii) the relative stability of the conjugated base, and these also have an influence on the experimental data obtained in solution. Accordingly, a more thorough theoretical calculation, taking into account the nature of the solvent, is in progress in our laboratory.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AM 250 spectrometer with trimethylsilane as internal standard. The abbreviations used are: s (singlet), d (doublet), t (triplet) and m (multiplet). − Mass spectra were measured using a Platform II Micromass Apparatus. − IR spectra were recorded using a Perkin−Elmer instrument. − Melting points were obtained with a Reichert Thermopan apparatus and are uncorrected. − Chromatographic separations were carried out on SDS silica gel 60 (70−200 μm). All reagents were used as purchased unless otherwise stated. Solvents were dried according to standard procedures. All reactions were performed under dry argon. The reagents were transferred by syringe.

General Procedure for the Synthesis of 1-Benzyl-1*H*-[1,2,4]triazol-4-ium Bromides 6c−e: The ω-bromoacetophenone compounds **11c−e** are commercially available. − A solution of ω-bromoacetophenone **11c−e** in anhydrous acetone (30 mL) was added at room temperature under argon to a solution of 1-benzyl-1*H*-[1,2,4]triazol (**10**, 10 mmol) in dry acetone (80 mL). The solution was warmed to reflux for 8 h. The crude product precipitated was filtered off and recrystallized from EtOH.

1-Benzyl-4-[2-(4-bromophenyl)oxoethyl]-1*H*-[1,2,4]triazol-4-ium Bromide (6c): Yield 3.32 g (76%), m.p. 200−201 °C. − ^{1}H NMR ($CDCl_3$/TMS): δ = 5.79 (s, 2 H, CH_2), 6.15 (s, 2 H, CH_2), 7.42−7.52 (m, 5 aromatic H), 7.89 (d, *J* = 8.5 Hz, 2 aromatic H), 8.00 (d, *J* = 8.5 Hz, 2 aromatic H), 9.18 (s, 1 aromatic H), 10.25 (s, 1 aromatic H). − ^{13}C NMR ($CDCl_3$/TMS): δ = 54.0, 54.8, 128.8, 128.8, 129.0, 130.2, 132.3, 132.5, 133.3, 143.6, 146.1, 189.8. − IR (KBr): $\tilde{\nu}$ = 3110 cm^{-1}, 2972, 1700, 1583, 1396, 1340, 1225, 1149, 992, 823. − MS (ES^+, cone 24); *m*/*z* (%): 356 (100) [M − Br], 358 (100) [M − Br], 91 (20) [$PhCH_2$]. − $C_{17}H_{15}Br_2N_3O$ (437.1): calcd. C 46.71, H 3.46, N 9.61; found C 46.92, H 3.44, N 9.52.

1-Benzyl-4-[2-(4-methoxyphenyl)oxoethyl]-1*H*-[1,2,4]triazol-4-ium Bromide (6d): Yield 1.82 g (47%), m.p. 160−165 °C. − ^{1}H NMR ($CDCl_3$/TMS): δ = 3.89 (s, 3 H, OCH_3), 5.79 (s, 2 H, CH_2), 6.12 (s, 2 H, CH_2), 7.17 (d, *J* = 8.9 Hz, 2 aromatic H), 7.44−7.48 (m, 5 aromatic H), 8.05 (d, *J* = 8.9 Hz, 2 aromatic H), 9.21 (s, 1 aromatic H), 10.28 (s, 1 aromatic H) − ^{13}C NMR ($CDCl_3$/TMS): δ = 53.7, 54.8, 55.8, 114.4, 128.8, 129.0, 130.2, 130.7, 133.3, 143.7, 146.1, 164.3, 188.6. − IR (KBr): $\tilde{\nu}$ = 3062 cm^{-1}, 2972, 1672, 1595, 1562, 1156, 1322, 1269, 1249, 1177, 1010, 828. − MS (ES^+, cone 35); *m*/*z* (%): 308 (100) [M − Br], 91 (15) [$PhCH_2$]. − $C_{18}H_{18}BrN_3O_2$ (388.3): calcd. C 55.68, H 4.67, N 10.82; found C 55.54, H 4.62, N 10.69

1-Benzyl-4-[2-(4-nitrophenyl)oxoethyl]-1*H*-[1,2,4]triazol-4-ium Bromide (6e): Yield 3.02 g (75%), m.p. 211−212 °C. − ^{1}H NMR ($CDCl_3$/TMS): δ = 5.80 (s, 2 H, CH2), 6.21 (s, 2 H, CH2), 7.43−7.52 (m, 5 aromatic H), 8.30 (d, *J* = 8.5 Hz, 2 aromatic H), 8.47 (d, *J* = 8.5 Hz, 2 aromatic H), 9.18 (s, 1 aromatic H), 10.24 (s, 1 aromatic H). − ^{13}C NMR ($CDCl_3$/TMS): δ = 54.4, 54.8, 124.2, 128.8, 129.0, 129.2, 129.8, 133.3, 138.1, 142.6, 146.1, 150.7, 189.8. − IR (KBr): $\tilde{\nu}$ = 3102 cm^{-1}, 3042, 2905, 1696, 1524, 1347, 1228, 1000, 857. − MS (ES^+, cone 21); *m*/*z* (%): 323 (100) [M − Br], 341 (10) [M + H_2O], 355 (40) [M + CH_3OH], 91 (15) [$PhCH_2$]. − $C_{17}H_{16}BrN_3O_2$ (403.2): calcd. C 50.64, H 3.75, N 13.89; found C 50.39, H 3.78, N 13.71.

General Procedure for the Synthesis of (1-Benzyl-1*H*-[1,2,4]triazol-4-io)(4-substituted benzoyl)(2,4,6-trinitrophenyl)methanides 7c−e and {4-[2-Oxo-2-(4-substituted phenyl)ethyl]-4*H*-[1,2,4]triazol-1-io}(phenyl)(2,4,6-trinitrophenyl)methanides 8c−e: A solution of freshly distilled Et_3N (5.6 mmol) in dry $CHCl_3$ (5 mL) was added to a stirred suspension of **6** (2.8 mmol) and picryl chloride (2.8 mmol) in dry $CHCl_3$ (30 mL) at O °C under Ar. The mixture was allowed to warm to room temperature, in the absence of light, over three hours. The solvent was evaporated and the deep purple crude product was chromatographed on SiO_2, using acetone-hexane (40:60) as eluent.

(1-Benzyl-1*H*-[1,2,4]triazol-4-io)(4-bromobenzoyl)(2,4,6-trinitrophenyl)methanide (7c) and {4-[2-(4-Bromophenyl)-2-oxoethyl]-4*H*-[1,2,4]triazol-1-io}(phenyl)(2,4,6-trinitrophenyl)methanide (8c): Yield 1.27 g (80%). − ^{1}H NMR ($CDCl_3$/TMS): δ = 5.32 (**7c**) and 5.40 (**8c**) (s, 2 H, CH_2), 7.02−7.43 (m, 9 aromatic H), 8.03 (**8c**) and 8.14 (**7c**) (s, 1 aromatic H), 8.46 (**7c**) and 8.68 (**8c**) (s, 2 aromatic H), 9.60 (**7c**) and 10.61 (**8c**) (s, 1 aromatic H). − IR (KBr): $\tilde{\nu}$ = 3084 cm^{-1}, 1700, 1598, 1527, 1448, 1305. − MS (ES^+, cone 32); *m*/*z* (%): 569 (100) [M + H], 567 (100) [M + H].

(1-Benzyl-1*H*-[1,2,4]triazol-4-io)(4-methoxybenzoyl)(2,4,6-trinitrophenyl)methanide (7d) and {4-[2-(4-Methoxyphenyl)-2-oxoethyl]-4*H*-[1,2,4]triazol-1-io}(phenyl)(2,4,6-trinitrophenyl)methanide (8d): Yield 0.88 g (61%). − ^{1}H NMR ($CDCl_3$/TMS): δ = 3.76 (**8d**) and 3.78 (**7d**) (s, 3 H, OCH_3), 5.30 (**8d**) and 5.42 (**7d**) (s, 2 H, CH_2), 6.65−6.72 (m, 2 aromatic H), 7.16−7.31 (m, 4 aromatic H), 7.44−7.47 (m, 3 aromatic H), 7.91 (**8d**) and 8.17 (**7d**) (s, 1 aromatic H), 8.47 (**7d**) and 8.63 (**8d**) (s, 2 aromatic H), 9.49 (**7d**) and 10.45 (**8d**) (s, 1 aromatic H). − IR (KBr): $\tilde{\nu}$ = 3089 cm^{-1}, 1703, 1603, 1520, 1454, 1299, 1250. − MS (ES^+, cone 63); *m*/*z* (%): 519 (30) [M + H], 472 (100) [M − NO_2], 91 (100) [$PhCH_2$].

(1-Benzyl-1*H*-[1,2,4]triazol-4-io)(4-nitrobenzoyl)(2,4,6-trinitrophenyl)methanide (7e) and {4-[2-(4-Nitrophenyl)-2-oxoethyl]-4*H*-[1,2,4]triazol-1-io}(phenyl)(2,4,6-trinitrophenyl)methanide (8e): Yield 1.16 g (78%). − ^{1}H NMR ($CDCl_3$/TMS): δ = 5.36 (**8d**) and 5.50 (**7d**) (s, 2 H, CH_2), 7.34−7.48 (m, 7 aromatic H), 7.95−8.04 (m, 2 aromatic H), 7.93 (**8d**) and 8.17 (**7d**) (s, 1 aromatic H), 8.55 (**7d**) and 8.70 (**8d**) (s, 2 aromatic H), 9.51 (**7d**) and 10.83 (**8d**) (s, 1 aromatic H). − IR (KBr): $\tilde{\nu}$ = 3050 cm^{-1}, 1705, 1607, 1525, 1453, 1307, 1309. − MS (ES^+, cone 35); *m*/*z* (%): 534 (100) [M + H], 487 (100) [M − NO_2], 91 (50) [$PhCH_2$].

General Procedure for the Synthesis of 1-Benzyl-6,8-dinitro-5-(4-substituted benzoyl)-1*H*-[1,2,4]triazolo[3,4-*a*]isoindoles 12c−e and 1-[2-Oxo-2-(4-substituted phenyl)ethyl]-5-phenyl-1*H*-[1,2,4]triazolo[5,1-*a*]isoindoles 13c−e: A solution of **7** and **8** (1.5 mmol) in DMSO (20 mL) was stirred under Ar in darkness at room temperature in the presence of piperidine (3 mmol) for 5 h. Initially, the solution had a deep purple color, which progressively turned to red. The solution was acidified with 3 N acetic acid and washed with water to obtain a red precipitate, which was filtered. The crude mixture was then separated by chromatography on SiO_2 using acetone/hexane (50:50) as eluent. Finally, each compound **12c−e** and **13c−e** was washed with boiling EtOH.

1-Benzyl-5-(4-bromobenzoyl)-6,8-dinitro-1*H*-[1,2,4]triazolo[3,4-*a*]-isoindole (12c): Yield 0.64 g (76%), m.p. 256−257 °C. − ^{1}H NMR (DMSO/TMS): δ = 5.96 (s, 2 H, CH_2), 7.45−7.74 (m, 9 aromatic H), 8.62 (s, 1 aromatic H), 8.74 (s, 1 aromatic H), 9.19 (s, 1 aromatic H). − ^{13}C NMR (DMSO/TMS): δ = 46.7, 106.1, 109.4, 118.1, 120.9, 122.9, 126.3, 127.7, 128.7, 129.1, 131.2, 131.4, 131.9, 134.1, 137.1, 137.6, 139.3, 146.4, 180.5. − IR (KBr): ṽ = 3118 cm^{-1}, 2927, 1732, 1604, 1551, 1524, 1502, 1291, 1252, 1171, 839. − MS (ES$^+$, cone 40); *m/z* (%): 520 (100) [M + H], 522 (100) [M + H]− $C_{23}H_{14}BrN_5O_5$ (520.3): calcd. C 53.18, H 2.71, N 13.46; found C 53.41, H 2.75, N 13.62.

1-Benzyl-5-(4-methoxybenzoyl)-6,8-dinitro-1*H*-[1,2,4]triazolo[3,4-*a*]-isoindole (12d): Yield 0.40 g (68%), m.p. 248−249 °C. − ^{1}H NMR (DMSO/TMS): δ = 3.87 (s, 3 H, OCH_3), 5.95 (s, 2 H, CH_2), 7.05 (d, *J* = 8.7 Hz, 2 aromatic H), 7.37−7.55 (m, 5 aromatic H), 7.82 (d, *J* = 8.7 Hz, 2 aromatic H), 8.62 (s, 1 aromatic H), 8.77 (s, 1 aromatic H), 9.19 (s, 1 aromatic H). − ^{13}C NMR (DMSO/TMS): δ = 49.7, 55.5, 105.3, 109.6, 113.7, 117.8, 119.8, 123.3, 127.7, 128.7, 129.1, 131.6, 133.5, 133.5, 134.1, 136.4, 138.8, 146.4, 162.8, 181.1. − IR (KBr): ṽ = 3119 cm^{-1}, 2925, 1731, 1607, 1553, 1527, 1504, 1311, 1252, 1172, 839. − MS (ES$^+$, cone 40); *m/z* (%): 472 (100) [M + H]. − $C_{24}H_{17}N_5O_6$ (471.4): calcd. C 61.13, H 3.64, N 14.86; found C 61.20, H 3.55, N 14.82.

1-Benzyl-6,8-dinitro-5-(4-nitrobenzoyl)-1*H*-[1,2,4]triazolo[3,4-*a*]-isoindole (12e): Yield 0.50 g (54%), m.p. 249−250 °C. − ^{1}H NMR (DMSO/TMS): δ = 5.96 (s, 2 H, CH_2), 7.33−7.53 (m, 5 aromatic H), 8.04 (d, *J* = 8.7 Hz, 2 aromatic H), 8.34 (d, *J* = 8.7 Hz, 2 aromatic H), 8.68 (s, 1 aromatic H), 8.79 (s, 1 aromatic H), 9.18 (s, 1 H). − ^{13}C NMR (DMSO/TMS): δ = 50.6, 107.8, 110.3, 119.2, 122.7, 123.5, 124.4, 129.6, 130.0, 131.3, 135.0, 135.5, 138.6, 140.5, 144.9, 147.4, 150.2, 180.2. − IR (KBr): ṽ = 3120 cm^{-1}, 2927, 1729, 1608, 1553, 1527.1520, 1502, 1307, 1254, 1169, 840. − MS (ES$^+$, cone 35); *m/z* (%): 487 (100) [M + H]− $C_{24}H_{17}N_5O_6$ (486.4): calcd. C 56.80, H 2.90, N 17.28; found C 56.54, H 3.01 N, 16.98.

1-[2-(4-Bromophenyl)-2-oxoethyl]-6,8-dinitro-5-phenyl-1*H*-[1,2,4]triazolo[5,1-*a*]isoindole (13c): Yield 0.27 g (82%), m.p. 236−237 °C. − ^{1}H NMR (DMSO/TMS): δ = 6.15 (s, 2 H, CH_2), 7.37−7.51 (m, 7 aromatic H), 7.67 (d, *J* = 8.5 Hz, 2 aromatic H), 8.71 (s, 1 aromatic H), 9.20 (s, 1 aromatic H), 9.59 (s, 1 aromatic H). − ^{13}C NMR (DMSO/TMS): δ = 54.1, 107.3, 121.2, 124.3, 125.1, 125.4, 128.0, 128.5, 128.9, 129.1, 131.9, 133.0, 134.4, 136.6, 138.0, 139.9, 140.4, 182.0. − IR (KBr): ṽ = 3152 cm^{-1}, 2925, 2954, 1706, 1623, 1571, 1526, 1446, 1357, 1308, 1251, 1148, 1074, 913, 734. − MS (ES$^+$, cone 35); *m/z* (%): 520 (100) [M + H], 522 (100) [M + H]. − $C_{23}H_{14}BrN_5O_5$ (520.3): calcd. C 53.18, H 2.71, N 13.46; found C 53.35, H 2.59, N 13.54.

1-[2-(4-Methoxyphenyl)-2-oxoethyl]-6,8-dinitro-5-phenyl-1*H*-[1,2,4]triazolo[5,1-*a*]isoindole (13d): Yield 0.17 g (78%), m.p. 229−230 °C. − ^{1}H NMR (DMSO/TMS): δ = 3.83 (s, 3 H, OCH_3), 6.14 (s, 2 H, CH_2), 7.00 (d, *J* = 8.8 Hz, 2 aromatic H), 7.37−7.50 (m, 5 aromatic H), 7.59 (d, *J* = 8.8 Hz, 2 aromatic H), 8.72 (s, 1 aromatic H), 9.19 (s, 1 aromatic H), 9.51 (s, 1 aromatic H). − ^{13}C NMR (DMSO/TMS): δ = 54.1, 55.4, 106.6, 107.2, 114.2, 120.9, 123.4, 125.2, 128.0, 128.5, 128.9, 129.5, 132.7, 133.3, 134.4, 136.0, 137.8, 162.1, 182.4. − IR (KBr): ṽ = 3154 cm^{-1}, 2924, 2853, 1729, 1623, 1595, 1576, 1526, 1501, 1455, 1360, 1304, 1254, 1152, 1059, 856. − MS (ES$^+$, cone 36); *m/z* (%): 472 (30) [M + H], 412 (100). − $C_{24}H_{17}N_5O_6$ (471.4): calcd. C 61.15, H 3.63, N 14.86; found C 61.15, H 3.58, N 14.89.

6,8-Dinitro-1-[2-(4-nitrophenyl)-2-oxoethyl]-5-phenyl-1*H*-[1,2,4]triazolo[5,1-*a*]isoindole (13e): Yield 0.09 g (67%), m.p. 278−279 °C. − ^{1}H NMR (DMSO/TMS): δ = 6.17 (s, 2 H, CH_2), 7.42−7.49 (m, 5 aromatic H), 7.79 (d, *J* = 8.0 Hz, 2 aromatic H), 8.31 (d, *J* = 8.0 Hz, 2 aromatic H), 8.73 (s, 1 aromatic H), 9.24 (s, 1 aromatic H), 9.64 (s, 1 aromatic H). − ^{13}C NMR (DMSO/TMS): δ = 54.1, 107.5, 107.9, 121.4, 124.2, 125.0, 128.0, 128.4, 128.6, 128.9, 133.3, 134.3, 137.0, 138.1, 140.7, 147.2, 148.8, 180.9. − IR (KBr): ṽ = 3148 cm^{-1}, 2924, 1725, 1598, 1549, 1524, 1515, 1499, 1301, 1251, 1159, 835. − MS (ES$^+$, cone 57); *m/z* (%): 525 (100) [M + K$^+$], 487 (80) [M + Na$^+$]. − $C_{24}H_{14}N_5O_6$ (486.4): calcd. C 56.80, H 2.90, N 17.28; found C 56.69, H 3.11, N 17.05.

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