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Regioselective Synthesis of New Biheterocyclic Triazepines

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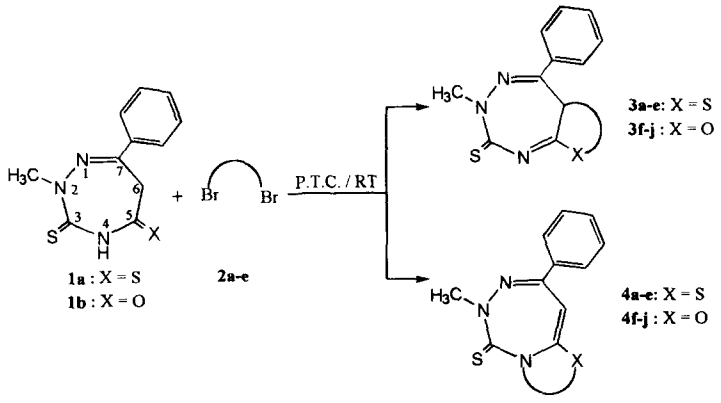
Abstract : Condensation of dihaloalkanes to 1,2,4-triazepine **1a** in the Phase Transfer Catalysis (P.T.C.) conditions provides efficient and facile access to biheterocyclic triazepines with high regioselectivity. In the same conditions, the triazepinone **1b** has been found to degradate after alkylation to give pyrazoles. © 1997 Published by Elsevier Science Ltd.

Recently, it has been demonstrated that heterocycles attached to seven membred rings show important biological activities.[1-3] In our previous studies, diazepines and triazepines have thus attracted a great deal of attention as starting material in the synthesis of fused heterocyclic systems of potential pharmacological activities.[4-9]

On further investigations in the field of heterocyclic systems, we now report a one-step synthesis of a new series of biheterocyclic triazepines by condensation of dibromoalkanes with the 2-methyl-7-phenyl-3,5-dithioxo-3,4,5,6-tetrahydro-2H-1,2,4-triazepine **1a**,[10] applying phase transfer catalysis conditions (Table 1).

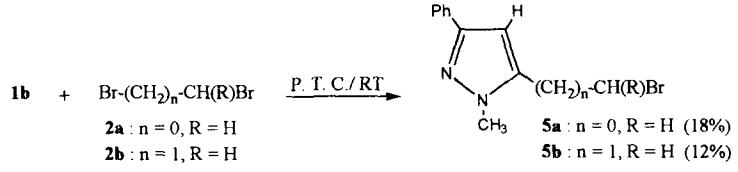
As it was first demonstrated by Jarrouse[11] and extensively developed by Makosza,[12] the P.T.C. technique is useful for most types of alkylations. Using dihaloalkanes, this method allows the preparation of cyclic systems.[13-15] However, its application to the synthesis of heterocyclic compounds is not well documented. We notice here particularly the preparation of thiazolo and thiazinothiouracil obtained with medium yield in hard conditions.[16] This leads us to discribe our regioselective one-step synthesis of new fused triazepines **4a-e** using this versatile technique.

At room temperature, 1,2,4-triazepines **1a-b** were treated with equimolar quantities of dibromoalkanes **2a-e** using the liquid-liquid P.T.C. technique. Since in such triazepines the thioxo and the oxo groups, the N-4 nitrogen and the C-6 carbon could be reactive towards alkylating agents,[17-18] the formation of two regioisomers is expected (scheme 1).



Scheme 1

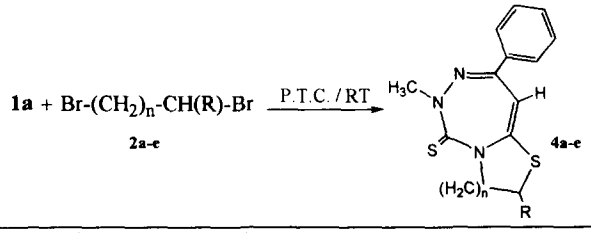
We have found that while the triazepine **1b** reacts only with dibromides **2a** and **2b** to provide the pyrazoles **5a** and **5b** in low yields[19] (scheme 2), the condensation of **1a** with all the alkyldibromides **2a-e** was achieved readily to afford good yields of the unique regioisomers **4a-e** (table 1).



Scheme 2

Furthermore, with unsymetrical dibromoalkane (entry 5) the direction of the condensation is unique and the sulfur atom is attached to the more sterically hindered end of the alkyldibromide to give the regioisomer **4e**.[19] The spectroscopic data of all the new fused 1,2,4-triazepines are consistent with the assigned structures mainly characterized by the =CH group which clearly appears in the ^{1}H-NMR and ^{13}C NMR spectra respectively as a singlet between 5.53 and 6.55 ppm, and a signal between 100.23 and 114.16 ppm (Table 1).

Table 1 : **Synthesis of new biheterocyclic triazepines**



Entry	n	R	Alkyl dihalide	Product	yield (%)	mp (°C)	Mass spectrum M^+ : m/z (%)	δ ^{1}H =C<u>H</u> (ppm)	δ ^{13}C =<u>C</u>H (ppm)
1	0	H	**2a**	**4a**	70	124-125	261 (100%)	5.53	100.23
2	1	H	**2b**	**4b**	81	oil	275 (100%)	5.90	103.04
3	2	H	**2c**	**4c**	85	oil	289 (82%)	6.09	112.78
4	3	H	**2d**	**4d**	72	110-111	303 (83%)	6.55	114.16
5	1	C_6H_5	**2e**	**4e**	77	oil	351 (100%)	5.97	103.00

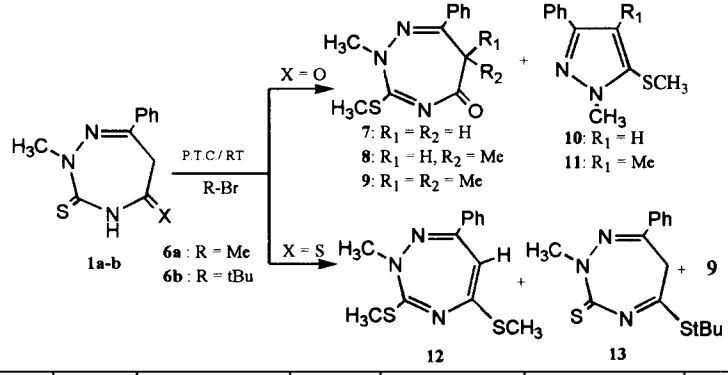
Spectrometric data of all compounds were in full accord with the structures proposed.

To account for this reactivity, it seemed reasonable to investigate the chemical behaviour of the triazepines **1a-b** towards monoalkylbromides **6a-b** in the same P.T.C.conditions (table 2).

Thus, either with alkylbromides or alkyldibromides the oxo group of the triazepine **1b** is inactive while the thioxo group at C-3 position is very reactive. It must be noticed here that after attacking this reactive center, the triazepine **1b** could readily rearrange to pyrazoles; due to the C-6 reactivity. On the other hand, **1b** was inactive towards either the dibromides **2c-e** or the alkylbromide **6b** regardless of the quantity used.

As for the triazepine **1a**, treated with either 1 or 2 equiv. of **6a**, the S-3, S-5-dimethylated triazepine **12**[20] is solely obtained. However, when using a large excess of **6a** a small amount of a C-6 dimethylated triazepine **9** was isolated besides **12** which is largely predominant. The triazepine **9** is presumably formed from **12** after oxydation of the C-5 mercapto group. In view of these facts, we can state that the thioxo groups at C-3 and C-5 positions are the most reactive centers in the triazepine **1a**. Nevertheless, when the alkylating agent is bulky (**6b** or **2a-e**), of the two thioxo groups only the one at C-5 position is alkylated.

Table 2 : **Alkylation of triazepines 1a-b with akylbromides 6a-b**



X	S	S	S	S	O	O	O	O
R-Br (equiv)	**6a** (1)	**6a** (2)	**6a** (3)	**6b**	**6a** (1)	**6a** (2)	**6a** (3)	**6b**
Product (Yield %)	**12** (35)	**12** (90)	**12** (85) **9** (10)	**13** (25)	7 (26) **10** (45)	7 (30) **8** (10) **10** (32) **11** (12)	7 (18) **9** (35) **10** (20) **11** (10)	-

All the products showed spectroscopic data consistent with their structures

In the light of all these results, it reveals that the thioxo groups at C-3 and C-5 positions are in general the most reactive centers in both triazepines **1a** and **1b**. This can be ascribed to their soft basic character. Moreover, the oxo group of **1b**, which is a hard basic center, presents no reactivity. On the other hand, despite its soft character the C-3 thioxo group is unreactive with bulky alkylating agents. This behaviour is likely due to a steric hindrance which holds up the alkylation of this soft basic center. Consequently, in the preparation of the new fused triazepines **4a-e**, only the C-5 thioxo group is attacked. It is noteworthy to emphasise that the ensuing cyclisation occurs at the N-4 nitrogen not at the C-6 carbon even the latter could disclose a certain soft basic character. We ascribe this to the fact that cyclisation at the C-6 carbon would probably lead to a thermodynamically unstable bicyclic system.

In conclusion, we have demonstrated a simple one-step synthesis of five new biheterocyclic triazepines *via* condensation of five alkyldibromides to the 1,2,4-triazepine **1a**. The preparation was carried out under the liquid-liquid P.T.C. conditions. The method was revealed to be efficient and highly regioselective. In contrast, the triazepine **1b** reacts in the same conditions only with nonbulky dibromides to afford the corresponding pyrazoles. Studying the reactive centers of both **1a** and **1b**, we have shown that the oxo group, which is a hard acid center, is unreactive while the C-5 thioxo group is the most reactive center ; due to its accessibility and its soft basic character.

General procedure for the preparation of 4a-e

A mixture of triazepine **1a** (1g, 4 mmol.) and benzyltriethylammonium chloride (0.18g, 0.8 mmol.) in 60 ml of benzene was stirred at room temperature. After 15 min, 50% aqueous NaOH (5 g) was added and followed by alkyldibromide (4mmol.). The mixture was stirred at room temperature for 6 hours, then diluted with water; the organic phase was separated and the aqueous layer was extracted twice with benzene. The combined organic solution was washed with water, dried (Na_2SO_4), filtred and concentrated in vacuo. The residue was purified with column chromatography (silica gel, hexane/AcOEt) to afford the bicyclic triazepines **4a-e**[19] with the corresponding yields.

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19. All new prepared compounds were fully identified by ^1H NMR (250 MHz, $CDCl_3$), ^{13}C NMR (62.89 MHz, $CDCl_3$) (*APT* and *DEPT*) and mass spectrometry. Some pertinent spectral data are as follows :
4a : ^1H NMR : δ = 3.48 (s, 3H, N-Me), 5.31 (s, 2H, N-CH_2-S), 5.53 (s, 1H, =C-H), 7.29-7.60 (m, 5H, Ph); ^{13}C NMR : δ = 44.16, 52.46, 100.23, 127.21, 128.47, 130.81, 135.42, 159.24, 165.72, 188.42; EI-MS : m/z = 261 (100%) (M^+). **4e :** ^1H NMR : δ = 3.57 (s, 3H, N-Me), 3.82 (dd, 1H, J = 12, 11, Ph-CH-S), 4.99 (dd, 1H, J = 11, 6, N-CH-), 5.44 (dd, 1H, J = 12, 6, N-CH-), 5.97 (s, 1H, =C-H), 7.21-7.72 (m, 10H, 2xPh); ^{13}C NMR: δ = 44.86, 50.23, 62.50, 103.00, 127.39, 128.12, 128.61, 128.67, 129.01, 131.05, 134.97, 135.42, 157.60, 166.09, 190.11; EI-MS : m/z = 351(100%) (M^+). **5a :** ^1H NMR : δ = 3.91 (s, 3H, N-Me), 4.43 (s, 2H, SCH_2Br), 6.54 (s, 1H, =C-H), 7.27-7.57 (m, 5H, Ph); ^{13}C NMR : δ = 37.48, 38.77, 106.34, 125.40, 127.68, 128.62, 131.02, 152.92, 152.51. EI-MS : m/z = 282 (42%) (M^+), m/z = 284 (41%) $(M+2)^+$.
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