Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Novel Synthesis of Imidazo[2,1-d][1,2,4]triazine and Imidazo[2,1-d][1,2,5]triazepine Derivatives via Ketene-N,N-acetal

Ahmed M. M. El-Saghier [a] , Abdussalam A. Maihub [b] & Hatif A. Al-Shirayda [b]

[a] Department of Chemistry, Faculty of Science, Sohag, Egypt

[b] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Arab Medical University, Benghazy, LIBYA

Published online: 21 Aug 2006.

To cite this article: Ahmed M. M. El-Saghier , Abdussalam A. Maihub & Hatif A. Al-Shirayda (1997) A Novel Synthesis of Imidazo[2,1-d][1,2,4]triazine and Imidazo[2,1-d][1,2,5]triazepine Derivatives via Ketene-N,N-acetal, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 27:14, 2433-2444, DOI: 10.1080/00397919708004107

To link to this article: http://dx.doi.org/10.1080/00397919708004107

SYNTHETIC COMMUNICATIONS, 27(14), 2433-2444 (1997)

A Novel Synthesis of Imidazo[2,1-d][1,2,4]triazine and Imidazo[2,1-d][1,2,5]triazepine Derivatives via Ketene-N,N-acetal

Ahmed M. M. El-Saghier *

Department of Chemistry, Faculty of Science, Sohag, Egypt.

Abdussalam A. Maihub and Hatif A. Al-Shirayda

Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Al-Arab Medical University, Benghazy, LIBYA.

Key Words: Imidazotriazine, Imidazotriazepine, Ketene-N,N-acetal.

The ketene-S,S-acetal *I* was prepared under phase-transfer catalysis (PTC) in benzene-carbonate two phase system using tetrabutylammonium bromide as the catalyst. Upon treatment with 1,2-diaminoethane, followed by hydrolysis with sodium methoxide, *I* gave 2-(2-oxopropylidene)imidazoline *III*. Bromination of *III* and replacement of bromine by hydrazine afforded 2-(1-hydazino-1,2-oxopropylidene)imidazoline *V*. Compound *V* was used as a precursor for the preparation of the previously unreported fused nitrogen heterocyclic ring system of imidazotriazine *VI*, *VIII*, *XI*, *XII* and imidazotriazepine *IX*, *X*.

Considerable interest has been shown in recent years[1,2] in studying the synthesis and reactions of various cyclic and acyclic ketene-S,S-, -N,S- and -N,N- acetal compounds[1-5]. The heterocyclic ketene-N,N-acetal derivatives[3-7] have attracted special attention, because they proved to be an efficient tool for the preparation of a wide variety of fused nitrogen heterocyclic compounds of biological importance[8-12].

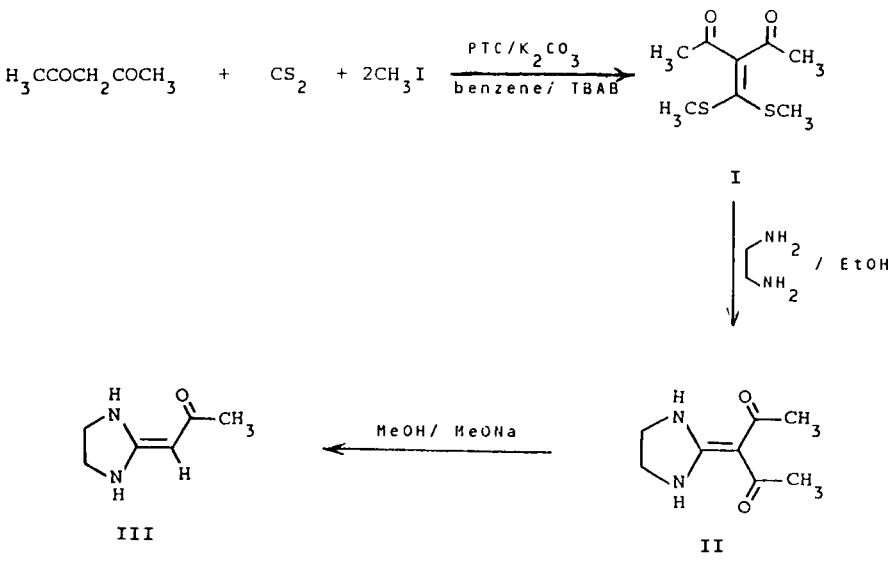
In connection with our work[13-16] on ketoketene or cyanoketene-S,S-acetals in heterocyclic synthesis using phase-transfer catalysis (PTC) we sought a novel synthesis for a new range of fused nitrogen heterocyclic compounds *VI-XII* (cf. scheme *III*). For this purpose, the previously unreported heterocyclic ketene-N,N-acetal *V* was prepared and utilized as akey intermediate. Compound *V* was prepared via a five-step procedure (scheme *I* and *II*). The initial ketene-S,S-acetal*I*was synthesised in excellent yield[13] using PTC conditions.

The mechanism of this reaction seems to be similar to those observed previously[12], namely, a Michael addition reaction, followed by elimination of two moles of methyl mercaptan. Subsequent displacement of the bromine in *IV* by hydrazine afforded 2-(1-hydrazino-1,2-oxopropylidene)imidazoline *V*,our key intermediate for the preparation of the new imidazotriazine compounds *VI*, *VIII*, *XI*, *XII* and imidazotriazepine compounds *IX*, *X* (scheme *III*).

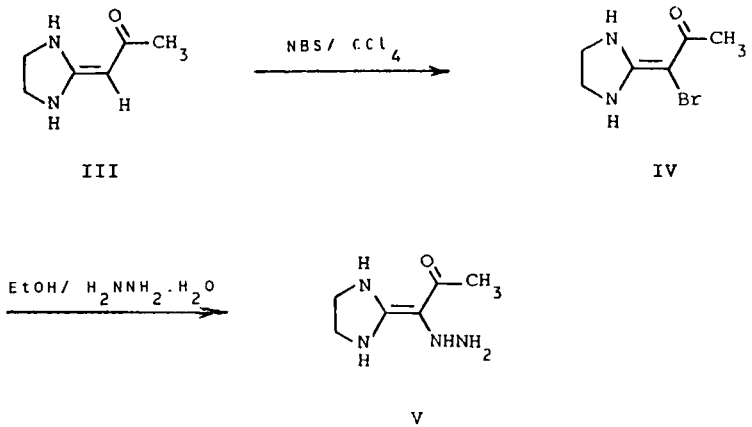
The imidazolidine *V* was treated with formaldehyde in boiling ethanol to give the imidazo [2,1-d][1,2,4]triazine *VI* .

The reaction of compound *V* with chloroacetyl chloride in acetic acid was shown to be temperature dependent. Thus, when compound *V* was stirred with chloroacetyl chloride[17] at room temperature, imidazolidine *VII* was obtained .

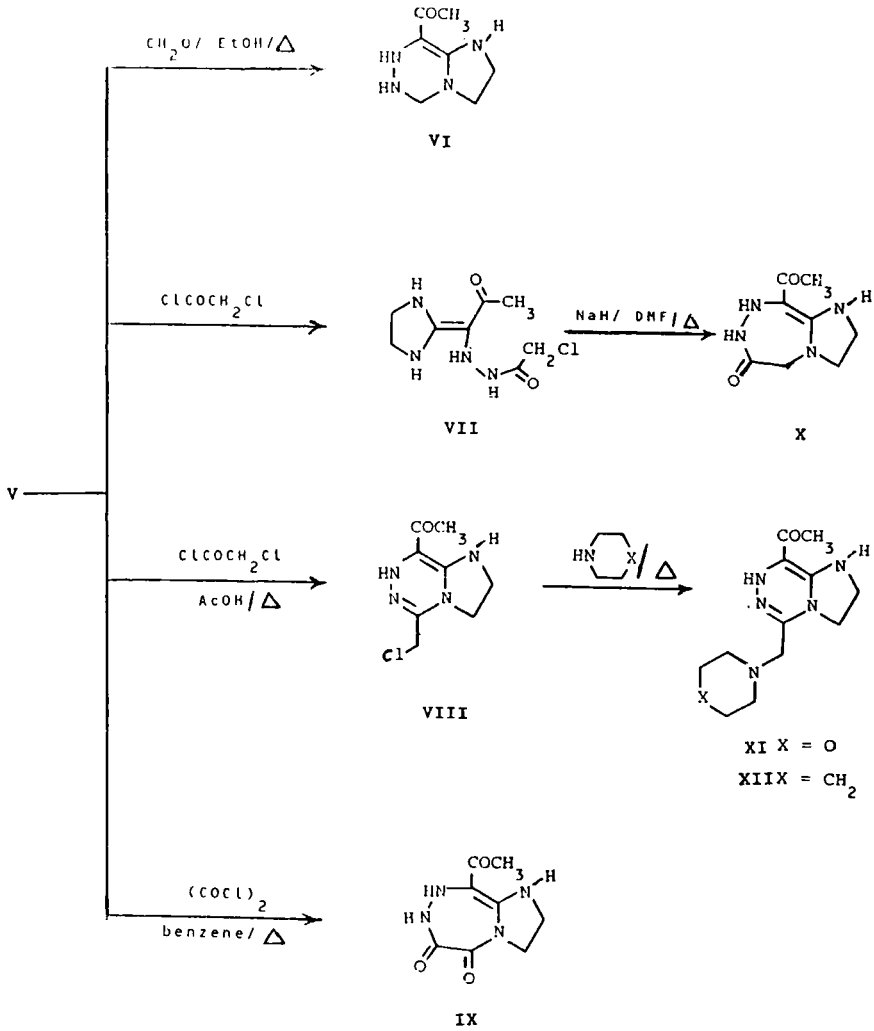
Under subsequent cyclization of compound *VII* in dimethyl formamide in the presence of sodium hydride gave the triazepin-6-(1H,7H,8H)-one *X*.



Scheme I



Scheme II



Scheme III

The reaction of compound *V* with chloroacetylchloride gave the imidazo[2,1-d][1,2,4]triazine *VIII* in excellent yield.

Further treatment of compound *VIII* with morpholine or piperidine furnished the corresponding 5-cyclic-aminomethyl derivatives *XI* and *XII* respectively (cf. scheme *III*).

The structure of the newly synthesised compounds was confirmed by elemental analyses and spectral data (cf.Tables *I*,*II*).

EXPERIMENTAL

All melting points were obtained on a Kofler melting point apparatus and were uncorrected. IR spectra were obtained (KBr disc.)on Nicolet 710 FT-IR spectrophotometer. ^{1}HNMR spectra were obtained on varian EM 360 L at 60 MHz using TMS as an internal standard. The elemental analyses were carried out on an elemental analyzer model 240 C.

2-(2-Oxopropylidine)imidazoline *(III)*

A micture of compound *II* (0.01 mol, 1.68 g) and NaOMe (1g of Na in 30 mL of MeOH) was refluxed for 4h., water(20 mL) was then added and the micture was extracted with $CHCl_3$(3x50 mL). The organic extract was dried (Na_2SO_4) and evaporated to give (1.49 g) of product *III*.

2-(1-Bromo-1,2-oxopropylidene)imidazolidine(*IV*)

To a well-stirred solution of compound *III* (0.01 mol, 1.26 g) in carbon tetrachloride (75 mL), N-bromosuccinimide (2.0 g, 0.01 mol)

Table *I*

Physical properties, yields and elemental analyses of compounds *II-XII*

Compound	M.P., °C Yield, %	Formula M.W.	Calculated/Found %C	 %H	 %N
II	198-200	$C_8H_{12}N_2O_2$	57.11	7.19	16.66
	91	168.11	57.12	7.21	16.59
III	155-157	$C_6H_{10}N_2O$	57.13	7.99	22.05
	89	126.16	57.15	7.91	22.13
IV	Semi-solid	$C_6H_9N_2OBr$	35.15	4.42	27.32
	93	205.05	35.22	4.38	27.27
V	169-171	$C_6H_{12}N_4O$	46.14	7.74	35.87
	78	156.19	45.95	7.66	35.60
VI	191-195	$C_7H_{12}N_4O$	49.98	7.19	33.31
	92	168.20	49.61	7.10	33.19
VII	233-235	$C_8H_{13}N_4O_2Cl$	41.30	5.63	24.08
	69	232.68	41.02	5.41	23.86
VIII	254-256	$C_8H_{11}N_4OCl$	44.76	5.16	26.10
	68	214.65	44.55	5.03	25.94
IX	>300	$C_8H_{10}N_4O_3$	45.53	4.77	26.55
	73	211.04	45.33	4.62	26.34
X	296-298	$C_8H_{12}N_4O_2$	48.97	6.13	28.55
	81	196.20	48.60	6.12	28.37
XI	216-218	$C_{12}H_{19}N_5O_2$	54.32	7.22	26.39
	62	265.30	53.90	7.11	26.23
XII	194-196	$C_{13}H_{21}N_5O$	59.29	8.04	26.59
	64	263.34	58.89	8.11	26.39

Table *II*

IR and ^{1}H NMR spectral data of synthesized compounds

Compound	νIR NH CH CO	d_6-DMSO, δ ppm
II	3281 2900, 2890 1650	9.85-9.65(br,2H,2NH);3.75(s,4H,2CH_2), 2.40 (s,6H,2CH_3).
III	3280 2980, 2920 1660	8.00-7.60(br,2H,2NH); 4.90(s,1H,=CH); 4.60(s,4H,2CH_2); 1.95 (s,3H,CH_3).
IV	3260 2970 1650	8.30-8.00(br,2H,2NH); 3.70(s,4H,2CH_2); 2.00(s,3H,CH_3).
V	a 3188 -- 1630	8.30-8.00(br,2H,2NH);4.40-4.10(br,3H, $NHNH_2$);3.60(s,4H,2CH_2);2.30(s,3H,CH_3)
VI	3420, 3313, 3259 2920 1654	7.40(s,1H,NH-imidazole); 6.30-5.80 (br,2H, NH-NH-triazine); 4.20-3.90 (m,2H,CH); 3.80-3.50(t,2H,CH-imida- zole); 3.20-3.00(t,2H,CH_2-triazine); 2.90(s,3H,CH_3).
VII	3200, 3190	8.90(br,2H,2NH-imidazole); 6.90(br,2H,

(continued)

Table II: Cont.

	2970, 2950	NH-NH); 4.20(s,2H,CH_2); 4.00-3.80(m,
	1679	2H,CH_2); 3.70-3.50(m,2H,CH_2); 2.80(s,
		3H,CH_3).
VIII	3450, 3200	9.20(br,1H,NH-imidazole); 7.20(s,1H,
	2970	NH-triazine); 4.40-4.20(t,2H,CH_2);
	1647	3.10(s,3H CH_3); 2.10(s,2H,CH_2Cl).
IX	3206, 3190	8.90(s,1H,NH); 6.90-6.70(br,2H,NH-NH);
	2980, 2960	4.30-4.10(t,2H,CH_2);4.00-3.80(m,2H,
	1691, 1650, 1603	CH_2), 3.10(s,3H,CH_3)
X	3200, 3180	9.10(s,1H,NH); 6.80-6.60(br,2H,NH-NH)
	2990, 2970	4.40(s,2H,CH_2-triazine); 4.20-4.00(d,
	1670, 1650	2H,CH_2);4.00-3.70(m,2H,CH_2);3.00(s,3H
		(CH_3).
XI	3420, 3200	9.00(br,1H,NH-imidazole); 7.20(s,1H,
	2980, 2960	NH-triazine); 4.40-4.20(t,2H,CH_2);
	1660	4.10-3.90(m,2H,CH_2);3.00(s,3H,CH_3);
		2.00(s,2H,CH_2-morphonyl); 1.90-1.70,
		1.60-1.50(m,8H,4CH_2-morpholine).
XII	3420, 3190	9.20(br,1H,NH-imidazole); 7.20(s,1H,
	2980, 2960	NH-triazine); 4.40-4.20(t,2H,CH_2);
	1650	4.10-3.90(m,2H,CH_2); 2.90(s,3H,CH_3);
		2.00(s,2H,CH_2-piperidyl); 1.90-1.70,
		1.60-1.40(m, 10H,5CH_2piperidine).

a: amino group 3309, 3224

was added in one portion and the mixture was stirred at room temprature for 3 h. The mixture was filtered through a small column of neutral alumina (2.0 g) and eluted with carbon teterachloride (50 mL), and the solvent was removed under vacuum to give (1.17 g) of product *IV* as a viscous liquid.

2-(1-Hydrazino-1,2-oxopropylidine)imidazoline (*V*)

A mixture of compound *IV* (4.0 mmol, 0.82 g) and hydrazine hydrate (4.20 mmol, 0.21 g) was stirred at room temperature in abs. EtOH (25 mL) for 1 h followed by heating under reflux for 15 min., and the mixture was concentrated to half its volume. On cooling, the precipitate was filtered off and crystallized from abs. EtOH to give (0.64 g) of compound *V*.

8-Acetyl-2,3,5-trihydro-1H,6H,7H-imidazo[2,1-d][1,2,4]triazine (*VI*)

Formaldehyde (5 mL) was added to a solution of compound *V* (1.56 g, 0.01 mol) in EtOH (50 mL) and the mixture was refluxed for 2 h. On cooling, the precipitate was filtered off and crystallized from MeOH affording (1.43 g) of white crystals of product *VI*.

General Procedure for the Reaction of *V* with Chloroacetyl Chloride

Chloroacetyl chloride (1.6 mL, 20 mmol) was dropwise added to a stirred cooled solution of *V* (10 mmol,1.56 g) in glacial AcOH (50 mL). The mixture was allowed to stir for 3 h at room temperature (for *VII*) or heated under reflux for 4 h (for *VIII*). Compound *VII* was obtained by addition of water (100 mL) to the reaction mixture

followed by filtration of the precipitated product and crystallization from EtOH to give white crystals, compound *VIII* was isolated by removing acetic acid in vacuo , then by adding water and sodium carbonate to achieve alkalinity and finally by filtering the solid formed.The crude product was then crystallized from dioxan.

9-Acetyl-2,3-dihydro-5H,6H-imidazo[2,1-d][1,2,3]triazepin-5,6-(1H,7H,8H)-dione *(IX)*

To a suspension of compound *V* (0.01 mol,1.56 g) in benzene (50 mL) was added oxalyl chloride (0.01 mol, 1.27 g) and the mixture was heated at reflux for 10 h. The solution was concentrated to dryness at reduced presure and the residue was treated with dilute ammonium hydroxide .The formed precipitate was then crystallized from EtOH to give (1.13 g) of white crystals of prouduct *IX*.

9-Acetyl-2,3-dihydro-6H-imidazo[2,1-d][1,2,5]triazepin-6-(1H,7H,8H)-one *(X)*.

Compound *VII* (5 mmol, 1.16 g) was dissolved in dry DMF (20 mL) and added dropwise to a cooled and stirred suspension of sodium hydride (0.30 g, 50% oil dispersion, 6 mmol) in DMF (60 mL). The mixture was allowed to warm to room temperature and stirred for 4 h. The reaction mixture was carefully diluted with water and extracted with ethyl acetate. The mixture was concentrated; (0.94 g) ofwhite crystals of prouduct *X* were isolated on cooling.

General procedure for the Reaction of *VIII* with Morpholine or Piperidine .

Compound *VIII* (5 mmol, 1.07 g) in morpholine (5 g, 60 mmol) and piperidine(5 g, 60 mmol) was stirred and heated at 100 °C for 12 h. Excess of the amine was removed in vacuo and the resulting residue directly crystallized from MeOH to give (0.66 g) of product *XI* and (0.68 g) of prouduct *XII*.

REFERENCES

1. Wang L.-B., Huang Z.-T.:Synthetic Communication 26(3),459 (1996)
2. Cheng Y., Wang M.-X., Gan W.-X.,Huang Z.-T. :Synthetic Communication 26(3),475 (1996).
3. Thuiller A., Vialle J.:Bull. Chem. Soc. Fr. 1398 (1959).
4. Kobayashi G., Matsuda Y., Natsuki R.:Chem. Pharm. Bull. 21, 921 (1973).
5. Rudorf W.-D., Augustin M.: J. Prakt. Chem. 319, 545 (1977).
6. Augustin M., Doelling W.: J. Prakt. Chem. 324, 3 (1982).
7. Nair M.D., Desai J.A.: Indian J. Chem. Sect.B 21, 4 (1982).
8. Rajappa S., Nair M.D., Sreenivasan R., Advani B.G.: Tetrahedron 36, 1673 (1982).
9. Huang Z.-T., Liu Z.-R.: Synthesis 357 (1987).
10. Gompper R., Toepfl W.: Chem. Ber. 95, 2961 (1962).
11. Rajappa S., Advani B.G.: Proc.Indian Acad. Sci.,[Ser.]:(Chem. Sci.) 91, 463 (1982). C.A.: 99, 70613 (1983).
12. Huang Z.-T., Shi X.: Synthesis 162 (1990).
13. El-Shafei A.K., El-Saghier A.M.M., Ahmed E.A.: Synthesis 152 (1994).

14. El-Saghier A.M.M.:Bull. Chem. Jpn. 66(7), 2011 (1993).

15. El-Shafei A.K., El-Saghier A.M.M., Sultan A.A., Soliman A.M.: Phosphorous, Sulfur and Silicon 72, 73 (1992).

16. El-Shafei A.K., Abdel-Ghany H.A., Sultan A.A., El-Saghier A.M.M.: Phosphorous, Sulfur and Silicon 73, 15 (1992).

17. Gatta F., Del Giudice M.R., Borioni A.: J. Heterocyclic Chem. 30, 11(1993).

(Received in the USA 06 February 1997)