Heterocycles from *N*-Ethoxycarbonylthioamides and Dinucleophilic Reagents. 3. Six- and Seven-Membered Rings with Two or Three Heteroatoms

Eleftherios Paul Papadopoulos* and Babu George

Department of Chemistry, The University of New Mexico, Albuquerque, New Mexico 87131

Received February 25, 1977

Reactions of *N*-ethoxycarbonylthioamides (1) with dinucleophilic reagents have allowed convenient preparation of a variety of heterocyclic compounds.[1] Depending upon the relative positions of the two nucleophilic sites in the reagent, these reactions have been observed to proceed in either of two manners. When the nucleophilic groups are adjacent, reaction occurs at both thiocarbonyl and carbonyl of 1 with elimination of H_2S and EtOH and formation of a five-membered, carbonyl-containing heterocycle. Thus, reactions with hydrazines and hydroxylamines yield triazolones and oxadiazolones, respectively.[1a] However, only the thiocarbonyl of 1 participates in reactions with 1,2-dinucleophilic reagents $H_2NCH_2CH_2YH$ and *o*-$H_2NC_6H_4YH$ (Y = NH, O, S), which take place with elimination of H_2S and ethyl carbamate and lead to dihydroimidazoles, -oxazoles, -thiazoles and benzimidazoles, -oxazoles, -thiazoles, respectively.[1b]

We have now found that reactions of 1 with 1,1-dinucleophilic reagents follow the former, whereas those with 1,3 or 1,4 such reagents the latter course. These and our earlier[1] results indicate that initial interaction between the thiocarbonyl of 1 and an amino group of the reagent results in elimination of H_2S and formation of C=N. The second nucleo-

Scheme I. Reactions of ArC(=S)NHCOOEt with 1,1-, 1,3-, and 1,4-Dinucleophilic Reagents

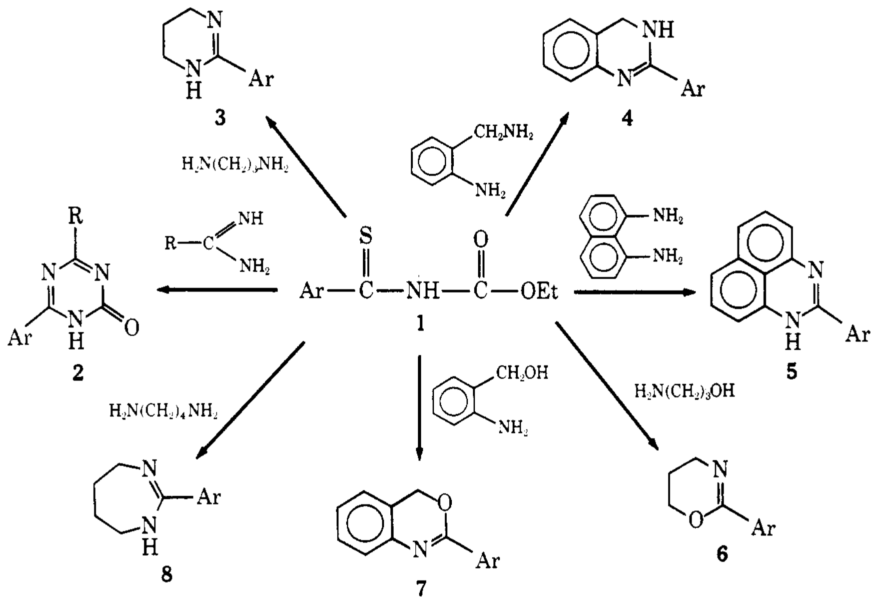
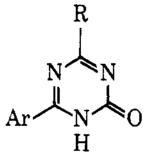


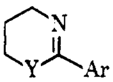
Table I.[a] 1,3,5-Triazin-2(1*H*)-ones (2)



Registry no.	R	Ar	Yield,[b] %	Mp, °C	IR (C=O), cm^{-1}	NMR, ppm
1917-36-8	Ph	4-MeC_6H_4[c]	50[d]	282.5–283.5[e,f]	1690	2.5 (s, 3), 7.3–7.7 (m, 5), 8.2–8.5 (m, 4), 12.0 (s, 1)[g]
1917-38-0	Ph	4-ClC_6H_4[c]	57[d]	286–288[e,h]	1695	7.5–7.8 (m, 5), 8.3–8.5 (m, 4), 11.3 (s, 1)[g]
62460-53-1	Ph	2-Pyrrolyl[c]	71[d]	312–313 dec[i]	1670	6.2 (m, 1), 7.1 (m, 1), 7.3–7.5 (m, 4), 8.3–8.5 (m, 2), 11.8 (br s, 1)
1917-40-4	Ph	Et[c]	55[d]	231–233[i,j]	1690	1.3 (t, 3), 2.6 (q, 2), 7.3–7.5 (m, 3), 8.0–8.2 (m, 2), 12.4 (br s, 1)
62460-54-2	$PhCH_2S$	4-MeC_6H_4[k]	87[l]	231–232.5[i]	1670	2.6 (s, 3), 4.9 (s, 2), 7.4 (s, 5), 7.5 (m, 2), 8.3 (m, 2), 11.6 (s, 1)[g]
62460-55-3	$PhCH_2S$	4-ClC_6H_4[k]	85[l]	217.5–218.5[i]	1660	4.9 (s, 2), 7.4 (s, 5), 7.7 (m, 2), 8.3 (m, 2), 11.6 (s, 1)[g]
62460-56-4	$PhCH_2S$	4-$EtOC_6H_4$[k]	76[l]	241.5–243[e]	1660	1.5 (t, 3), 4.3 (q, 2), 4.8 (s, 2), 7.2 (m, 2), 7.4 (s, 5), 8.4 (m, 2), 11.5 (s, 1)[g]

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or recrystallized product with melting point lower than that of the pure compound by not more than 10 °C. [c] Reaction run in EtOH with EtONa used to liberate $PhC(=NH)NH_2$ from its HCl salt. [d] The reaction mixture was evaporated to one-half its volume, chilled, and filtered. [e] Recrystallized from *n*-BuOH. [f] Lit. mp 284 °C: E. Degener, H.-G. Schmelzer, and H. Holtschmidt, *Angew. Chem., Int. Ed. Engl.*, 5, 960 (1966). [g] In CF_3COOD. [h] Lit. mp 287–288 °C: ref in *f*. [i] Recrystallized from EtOH. [j] Lit. mp 230 °C: ref in *f*. [k] Reaction run in MeOH with MeONa used to liberate $PhCH_2SC(=NH)NH_2$ from its HCl salt. [l] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed with cold H_2O.

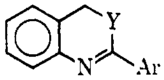
Table II.[a] 1,4,5,6-Tetrahydropyrimidines (3) and 5,6-Dihydro-4*H*-1,3-oxazines (6)



Registry no.	Y	Ar	Yield,^{b} %	Mp (bp), °C	NMR, ppm
62460-57-5	NH	4-MeC$_6$H$_4$^{c}	77^d	116.5–118.5^e	1.7 (m, 2), 2.3 (s, 3), 3.3 (m, 4), 5.8 (s, 1), 7.1 (m, 2), 7.6 (m, 2)
46313-35-3	NH	4-MeOC$_6$H$_4$^{c}	63^d	131.5–133^f	1.6 (m, 2), 3.3 (m, 4), 3.7 (s, 3), 5.9 (s, 1), 6.7 (m, 2), 7.5 (m, 2)
26131-42-0	NH	2-Thienyl^c	94^g	184–186^{h,i}	1.7 (m, 2), 3.4 (m, 4), 7.2 (m, 1), 7.6 (m, 2)
62460-58-6	NH	2-Pyrrolyl^j	94^d	163–164.5^e	1.7 (m, 2), 3.3 (m, 4), 5.9 (m, 1), 6.4 (m, 1), 6.6 (m, 1), 7.9 (s, 2)
10431-91-1	O	Et^c	60^k	(70–71 (43 Torr))^l	1.0 (t, 3), 1.5–2.2 (m, 4), 3.2 (m, 2), 3.9 (m, 2)
43221-69-8	O	4-MeC$_6$H$_4$^{j}	50^k	(121–123 (2 Torr))^{m,n}	1.8 (m, 2), 2.3 (s, 3), 3.4 (m, 2), 4.2 (m, 2), 7.0 (m, 2), 7.5 (m, 2)
62460-59-7	O	4-BrC$_6$H$_4$^{c}	63^o	73.5–75^{p,q}	1.9 (m, 2), 3.5 (m, 2), 4.3 (m, 2), 7.7 (m, 4)
62460-60-0	O	2-Pyrrolyl^j	60^d	139–141^r	1.8 (m, 2), 3.4 (m, 2), 4.2 (m, 2), 5.9 (m, 1), 6.3 (m, 1), 6.7 (m, 1), 9.8–11.7 (br s, 1)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or recrystallized material with melting point lower than that of the pure compound by not more than 10 °C. [c] Reaction run in THF. [d] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed with cold water. [e] Recrystallized from benzene–petroleum ether (bp 60–75 °C). [f] Recrystallized from EtOAc–petroleum ether (bp 60–75 °C). [g] The residue obtained as in *d* was first washed with aqueous NaOH and then with H$_2$O. [h] Recrystallized from EtOAc. [i] Lit. mp 183–185 °C: J. W. McFarland, L. H. Conover, H. L. Howes, Jr., J. E. Lynch, D. R. Chisholm, W. C. Austin, R. N. Cornwell, J. C. Danilewicz, W. Courtney, and D. H. Morgan, *J. Med. Chem.*, **12**, 1066 (1969). [j] Reaction run in EtOH. [k] After the solvent had been distilled under reduced pressure, the liquid residue was extracted with five 20-mL portions of petroleum ether (bp 35–60 °C) and the product was isolated from the extract by removal of the solvent and distillation of the new residue under reduced pressure. [l] Lit. bp 70 °C (43 Torr): A. Levy and M. Pitt, *Polym. Lett.*, **5**, 881 (1967). [m] Lit. bp 122–124 °C (2 Torr): Z. Eckstein, K. Majewski, and P. Gluzinski, *Rocz. Chem.*, 36, 73 (1962). [n] Picrate (recrystallized from EtOH): mp 137–138 °C. Lit. mp 134–135 °C: ref in *m*. [o] The residue obtained as in *g* was extracted repeatedly with boiling petroleum ether (bp 60–75 °C) and the decanted extracts were chilled to yield the product. [p] Recrystallized from petroleum ether (bp 60–75 °C). [q] Lit. bp 130 °C (2.5 Torr): ref in *m*. [r] Recrystallized from aqueous EtOH.

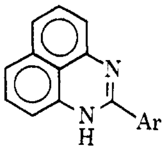
Table III.[a] 3,4-Dihydroquinazolines (4) and 4*H*-1,3-Benzoxazines (7)



Registry no.	Y	Ar	Yield,^{b,c} %	Mp, °C	NMR, ppm
62460-61-1	NH	4-MeC$_6$H$_4$^{d}	50	153–155^e	2.3 (s, 3), 4.6 (s, 2), 7.0 (m, 4), 7.3 (m, 2), 7.9 (m, 2)
39696-30-5	NH	4-MeOC$_6$H$_4$^{d}	38	177–179^{e,f}	3.8 (s, 3), 4.6 (s, 2), 7.0 (m, 6), 7.9 (m, 2)
62460-62-2	O	4-MeC$_6$H$_4$^{g}	64	104–105.5^h	2.3 (s, 3), 5.4 (s, 2), 7.2 (m, 4), 7.3 (m, 2), 7.9 (m, 2)
62460-63-3	O	4-MeOC$_6$H$_4$^{g}	67	142–143^{h,i}	3.8 (s, 3), 5.4 (s, 2), 7.3 (m, 4), 7.1 (m, 2), 8.1 (m, 2)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed successively with cold 10% aqueous NaOH and cold H$_2$O. [c] Crude or recrystallized material with melting point lower than that of the pure compound by not more than 7 °C. [d] Reaction run in MeOH with MeONa used to liberate *o*-H$_2$NC$_6$H$_4$CH$_2$NH$_2$ from its dihydrochloride salt. [e] Recrystallized from aqueous EtOH. [f] Lit. mp 178–179 °C: M. Lora-Tamayo, R. Madroñero, and G. Garcia Muñoz, *Chem. Ber.*, 94, 208 (1961). [g] Reaction run in THF. [h] Recrystallized from petroleum ether (bp 60–75 °C). [i] Lit. mp 138–142 °C: B. Witkop, J. B. Patrick, and H. M. Kissmary, *Chem. Ber.*, **85**, 949 (1952).

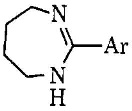
Table IV.[a] Perimidines (5)



Registry no.	Ar	Yield,^{b,c} %	Mp, °C	NMR, ppm
15666-84-9	Ph^d	95	186–188^{e,f}	6.6 (m, 2), 7.1 (m, 4), 7.5 (m, 3), 8.0 (m, 2), 10.6 (s, 1)
62460-64-4	4-*i*-PrC$_6$H$_4$^{g}	83	191.5–193.5 dec^{h,i}	1.2 (d, 6), 2.9 (m, 1), 6.5 (m, 1), 6.6 (m, 1), 7.1 (m, 4), 7.3 (m, 2), 7.9 (m, 2), 10.5 (s, 1)
25110-46-7	4-MeOC$_6$H$_4$^{g}	86	205–207 dec^{h,i,j}	3.8 (s, 3), 6.6 (m, 1), 6.7 (m, 1), 7.1 (m, 6), 8.0 (m, 2), 10.6 (s, 1)
62460-65-5	2-Thienyl^d	88	166–168^e	6.6 (m, 2), 7.1 (m, 5), 7.7 (m, 1), 7.9 (m, 1), 10.8 (s, 1)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in this table. [b] Crude or recrystallized material with melting point lower than that of the pure compound by not more than 10 °C. [c] The reaction mixture was evaporated to dryness under reduced pressure and the residue was washed with water. [d] Reaction run in benzene. [e] Recrystallized from cyclohexane. [f] Lit. mp 188 °C: W. A. Mosher and T. E. Banks, *J. Org. Chem.*, 36, 1477 (1971). [g] Reaction run in THF. [h] Recrystallized from benzene. [i] Formation of black tar upon melting hinders exact determination of melting point. [j] Lit. mp 205 °C [F. Sachs and M. Steiner, *Chem. Ber.*, 42, 3674 (1909)]; 210–211 °C dec [ref in *f*]; 212 °C [N. P. Buu-Hoi, P. Jacquignon, and M. Marty, *Bull. Soc. Chim. Fr.*, 461 (1960)].

Table V.[a] 4,5,6,7-Tetrahydro-1*H*-1,3-diazepines (8)



Registry no.	Ar[b]	Yield,[c,d] %	Mp,[e] °C	NMR,[f] ppm
62460-50-8	4-MeC_6H_4	40	115–116.5	1.8 (m, 4), 2.3 (s, 3), 3.5 (m, 4), 4.8 (s, 1), 7.1 (m, 2), 7.6 (m, 2)
62460-51-9	4-BrC_6H_4	52	137.5–139	1.8 (m, 4), 3.5 (m, 4), 4.7 (s, 1), 7.5 (s, 4)
62460-52-0	4-ClC_6H_4	57	132.5–134	1.8 (m, 4), 3.5 (m, 4), 4.8 (s, 1), 7.3 (m, 2), 7.5 (m, 2)
62505-86-6	2-Pyrrolyl	25	141.5–142.5	1.7 (m, 4), 3.4 (m, 4), 6.2 (m, 1), 6.4 (m, 1), 6.9 (m, 1), 7.2 (s, 2)

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all compounds listed in this table. [b] Reactions run in THF. [c] The reaction mixture was evaporated to dryness under reduced pressure and the residue was boiled repeatedly with petroleum ether (bp 60–75 °C). Chilling of the decanted extracts yielded the product. [d] Recrystallized material with melting point lower than that of the pure compound by not more than 5 °C. [e] Recrystallization from petroleum ether (bp 60–75 °C). [f] In $CDCl_3$.

philic group attacks the ester carbonyl of the intermediate[1a] only if the possibility exists for a five- or six-membered, carbonyl-containing ring to be formed. When this ring would be seven-membered or larger, the second nucleophilic group reacts instead with the C=N of the intermediate to cause elimination of ethyl carbamate and formation of a ring incorporating only the thiocarbonyl carbon atom of **1**.

Thus, *N*-ethoxycarbonylthioamides (**1**) react with benzamidine or 2-benzyl-2-thiopseudothiourea following the first route to yield 1,3,5-triazin-2(1*H*)-ones (**2**, Table I). On the other hand, the second pathway is followed in reactions of **1** with 1,3-diaminopropane, *o*-aminobenzylamine, or 1,8-diaminonaphthalene and the products are 1,4,5,6-tetrahydropyrimidines (**3**, Table II), 3,4-dihydroquinazolines (**4**, Table III), or perimidines (**5**, Table IV), respectively. Use of 3-amino-1-propanol or *o*-aminobenzyl alcohol leads correspondingly to 5,6-dihydro-4*H*-1,3-oxazines (**6**, Table II), or 4*H*-1,3-benzoxazines (**7**, Table III). Finally, treatment of **1** with 1,4-diaminobutane results in convenient formation of 4,5,6,7-tetrahydro-1*H*-1,3-diazepines (**8**, Table V) (Scheme I).

The structures of these products were established by preparation of known members of the various series, as well as by spectroscopic (IR, NMR) and microanalytical data. As before,[1] the reactions were generally run in tetrahydrofuran, ethanol, or methanol, at reflux, and their progress was followed by monitoring the H_2S evolution. Because in some cases (especially those involving use of 1,4-diaminobutane), the NMR spectrum of the crude product indicated incomplete ring closure by the time H_2S had ceased to be evolved, refluxing of the reaction mixture was usually allowed to proceed for an additional 2–3 h or simply overnight.

The reactions described in this paper, characterized by simplicity of operation, ease of product isolation and, in most cases, good yield, further establish the usefulness of *N*-ethoxycarbonylthioamides as starting materials for the synthesis of heterocyclic compounds.

Experimental Section[2]

***N*-Ethoxycarbonylthioamides (1)** were prepared as reported earlier.[1,3]

General Procedure for Preparation of Compounds 2–8. A solution of 0.010 mol of **1** and 0.012 mol of the dinucleophilic reagent in 10 mL of solvent (0.020 mol of reagent and 50 mL of solvent for compounds **8**) was refluxed until evolution of H_2S had ceased (PbOAc paper) and for an additional 2–3 h (or overnight). The reaction mixture was then treated as indicated in Tables I–V.

Acknowledgments. Financial support by the Research Corporation, the Research Allocations Committee of The University of New Mexico, and the Department of Chemistry of The University of New Mexico is gratefully acknowledged.

Registry No.—**1** (Ar = 4-MeC_6H_4), 57774-66-0; **1** (Ar = 4-ClC_6H_4), 57774-74-0; **1** (Ar = 2-pyrrolyl), 37488-43-0; **1** (Ar = Et), 59812-12-3; **1** (Ar = 4-$EtOC_6H_4$), 57774-73-9; **1** (Ar = 4-$MeOC_6H_4$), 57774-72-8; **1** (Ar = 2-thienyl), 51774-59-5; **1** (Ar = 4-BrC_6H_4), 57774-75-1; **1** (Ar = Ph), 5499-31-0; **1** (Ar = 4-*i*-PrC_6H_4), 57774-68-2; benzenecarboximidamide, 618-39-3; benzyl carbamimidothioate, 621-85-2; 1,3-propanediamine, 109-76-2; 2-aminobenzenemethanamine, 4403-69-4; 1,8-naphthalenediamine, 479-27-6; 3-amino-1-propanol, 156-87-6; 2-aminobenzenemethanol, 5344-90-1; 1,4-butanediamine, 110-60-1.

References and Notes

(1) (a) B. George and E. P. Papadopoulos, *J. Org. Chem.*, **41**, 3233 (1976); (b) *ibid.*, **42**, 441 (1977).

(2) Melting points were determined in capillaries by use of a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 337 spectrophotometer using mineral oil mulls. NMR spectra were obtained on a Varian EM360 spectrometer using solutions in hexadeuteriodimethyl sulfoxide (unless otherwise indicated) with tetramethylsilane as internal standard.

(3) E. P. Papadopoulos, *J. Org. Chem.*, **38**, 667 (1973); **39**, 2540 (1974); **41**, 962 (1976).