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Novel Fused Heterocycles: Synthesis and Activity of 5,6-Dihydro-7-thia-1,3,3a,5-tetraazainden-4-one and 1-Thia-3,4a,9-triazafluoren-4-one Derivatives

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Summary. Thiatetraazaindenone derivatives were synthesized by reaction of 3-substituted 1,2,4-triazole-5-thiols with N-substituted N-chloromethyl carbamoyl chlorides. A series of thiatriazafluorenone derivatives were also prepared by reaction of benzimidazole derivatives with the same substrate. Some of the new compounds show fungicidal, herbicidal, and insecticidal activity.

Keywords: Heterocycles; Cyclization; Thiatetraazaindenones; Thiatriazafluorenones.

Introduction

Fused benzimidazoles of the type 6-5-6 with one or two additional heteroatoms have shown good biological activities and have found widespread application [1]. Condensed triazole derivatives have attracted much attention in recent years for the same reason [2]. These facts prompted us to synthesize new fused heterocyclic compounds to develop bioactive lead compounds of high potency. In this study, the synthesis of novel fused heterocyclic compounds of the title type is described.

Results and Discussion

Reactions of N-substituded N-chloromethyl carbamoyl chlorides (**1**, [3]) with benzimidazole-2-thiol (**2**) or 3a,4,5,6,7,7a-hexahydro-1*H*-benzimidazole-2-thiol (**3**) [4] were carried out to give the corresponding derivatives **4** and **5** (Scheme 1). Their structures are in accordance with the data given in the experimental part.

Compounds **8a–i** were synthesized by reaction of **1** with 3-substituted 1,2,4-triazole-5-thiols **6** in *DMF* solution at room temperature (Scheme 2). It has been reported that N-1 and N-2 are more basic than N-4 in *s*-triazoles [5, 6]; therefore, the former are attacked preferably by the electrophilic carbonyl group under basic conditions [7]. It has also been proven that the chloromethyl group of **1** reacts with

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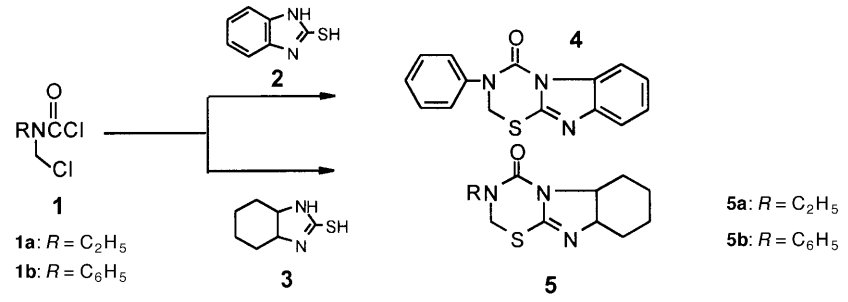
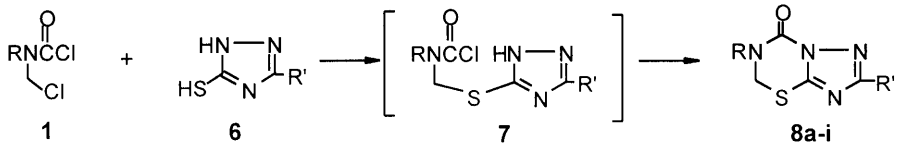


Scheme 1

certain nucleophiles (*e.g.* alcohols, thiols, *etc.*) in preference to the carbonyl chloride group [8]. Considering both the difference in reactivity between the chloromethyl and the carbamoyl chloride group and the fact that thiols are generally stronger nucleophilic agents than amines, we suggest that the cyclization reaction proceeds such that the chloromethyl group of **1** is first attacked by the sulfur of the triazole to form the intermediate **7**; then the carbamoyl group reacts with N-1 of the triazole (see Scheme 2). No formation of by-products could be observed during the reaction. Spectroscopic evidence proved the products to be cyclic triazolo-thiadiazinone derivatives.



8a: $R = C_6H_5$, $R' = H$ **8b**: $R = C_6H_5$, $R' = CH_3$ **8c**: $R = C_6H_5$, $R' = (CH_3)_3C$
8d: $R = C_6H_5$, $R' = 4\text{-}CH_3OC_6H_4$ **8e**: $R = C_6H_5$, $R' = 4\text{-}C_2H_5C_6H_4$ **8f**: $R = C_6H_5$, $R' = 2,4\text{-}di\text{-}ClC_6H_3$
8g: $R = C_6H_5$, $R' = 3,5\text{-}di\text{-}CH_3C_6H_3$ **8h**: $R = C_2H_5$, $R' = (CH_3)_3C$ **8i**: $R = C_2H_5$, $R' = 4\text{-}CH_3OC_6H_4$

Scheme 2

Some compounds were screened for insecticidal, fungicidal, and herbicidal activities. Compound **4** showed moderate fungicidal activities at 50 g/dm^3 against *Fusarium oxysporum f. vasinfectum*, *Alternaria solani*, *Trichoderma yiride*, *Botrytis cinerea*, and *Rhizoctoni solani*. Compound **8f** had 100% insecticidal activity at 300 g/dm^3 against *Tetranychus bimaculatus* Harvey, compound **8h** showed insecticidal activity ($IC_{50} = 400$ g/dm^3) against *Aphis laburni* Kaltenbach and an inhibitory activity ($IC_{50} = 400$ g/dm^3) against *Triticum vulgare* Host.

Experimental

All melting points were taken on a digital melting point apparatus made in Shanghai and are uncorrected. Infrared spectra were measured using a Nicolet 20sx Ft-IR instrument. Mass spectra were recorded on a Hitachi M80 instrument. ^{1}H NMR spectra were obtained using a Bruker-AC500 (500 MHz) spectrometer in $CDCl_3$ or *DMSO* using *TMS* as the internal standard. The analyses for elemental composition were undertaken with an Italy MOD.1106 analyzer at the Analysis Center of the East China University of Science and Technology; their results agreed satisfactorily with the calculated values.

3-Phenyl-2,3-dihydro-1-thia-3,4a,9-triaza-fluoren-4-one (**4**; $C_{15}H_{11}N_3OS$)

To a solution of 1.50 g **2** (0.01 mol) in 30 cm^3 *THF*, a solution of 2.04 g **1b** (0.01 mol) in 10 cm^3 benzene was added dropwise with stirring at room temperature. Then, 2.04 g triethylamine (0.022 mol) were added dropwise, and the mixture was refluxed for 4–5 h. After cooling to room temperature, the precipitate was filtered and washed with ethyl acetate. The filtrate was collected, and the solvent was removed under reduced pressure leaving a crude product. Crystallization from ethanol afforded a colorless product.

Yield: 2.31 g (82%); m.p.: 130–132°C; IR (KBr): $\nu = 1715$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 5.13 (s, 2H), 7.26–7.47 (m, 5H), 7.49 (m, 2H), 7.67 (dd, 1H), 8.07 (dd, 1H) ppm; MS (EI, 70 eV): *m/z* (%) = 281 (100, M^+), 177 (18), 105 (90), 104 (24), 77 (20).

3-Ethyl-2,3,4b,5,6,7,8,8a-octahydro-1-thia-3,4a,9-triaza-fluoren-4-one (**5a**; $C_{11}H_{17}N_3OS$)

To a solution of 1.56 g **3** (0.01 mol) in 30 cm^3 acetone, 1.54 g **1a** (0.01 mol) were added dropwise at room temperature, followed by 2.04 g triethylamine (0.022 mol). After addition the mixture was stirred at 40–50°C for 4–5 h. After cooling to 5°C, 20 cm^3 ice water were added, and stirring was continued at 0–10°C for 0.5 h. The solid was collected by filtration, washed with H_2O, and dried.

Yield: 1.55 g (65%); m.p.: 158–159°C; IR (KBr): $\nu = 1675$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.23 (t, 3H, $J = 7.1$ Hz), 1.46–1.50 (m, 4H), 1.85–1.88 (m, 2H), 2.34 (d, 2H, $J = 11.3$ Hz), 2.70 (d, 2H, $J = 10.4$ Hz), 3.28–3.40 (m, 2H), 3.53 (m, 1H), 3.60 (m, 1H), 4.16 (d, 1H, $J = 12.7$ Hz), 4.93 (d, 1H, $J = 12.7$ Hz) ppm; MS (EI, 70 eV): *m/z* (%) = 239 (100, M^+), 197 (12), 185 (37), 183 (64), 168 (11), 141 (18), 127 (18), 81 (33), 58 (50), 42 (81).

3-Phenyl-2,3,4b,5,6,7,8,8a-octahydro-1-thia-3,4a,9-triaza-fluoren-4-one (**5b**; $C_{15}H_{17}N_3OS$)

The synthesis of **5b** proceeded similar to that of **4**. A colorless product was obtained.
Yield: 2.49 g (87%); m.p.: 176–178°C; IR (KBr): $\nu = 1670$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.31–1.51 (m, 4H), 1.79–1.82 (m, 2H), 2.30 (d, 2H, $J = 11.07$ Hz), 2.77 (d, 2H, $J = 12.0$ Hz), 3.29–3.42 (m, 2H), 4.55 (d, 1H, $J = 12.8$ Hz), 5.25 (d, 1H, $J = 12.8$ Hz), 7.19–7.35 (m, 5H) ppm; MS (EI, 70 eV): *m/z* (%) = 287 (29, M^+), 182 (5), 119 (5), 105 (100), 104 (26), 41 (11).

General procedure for the preparation of 5,6-dihydro-7-thia-1,3,3a-5-tetraaza-inden-4-ones **8**

A mixture of 0.01 mol **1**, 0.01 mol **5**, and 3.04 g (0.022 mol) anhydrous K_2CO_3 in 10 cm^3 N,N-dimethylformamide was stirred at room temperature for 1–2 h and then diluted with water. The resulting precipitate was collected, washed with water, and the crude product was crystallized from ethanol.

5-Phenyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8a**; $C_{10}H_8N_4OS$)

Yield: 1.88 g (78%); m.p.: 188–189°C; IR (KBr): $\nu = 1725$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 5.49 (s, 2H), 7.39–7.52 (m, 5H), 8.29 (s, 1H); MS (EI, 70 eV): *m/z* (%) = 232 (41, M^+), 132 (20), 113 (46), 105 (100), 104 (65), 86 (12), 57 (19), 50 (27).

2-Methyl-5-phenyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8b**; $C_{11}H_{10}N_4OS$)

Yield: 2.0 g (81%); m.p. 222–223°C; IR (KBr): $\nu = 1730$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 2.44 (s, 3H), 5.10 (s, 2H), 7.33–7.46 (s, 5H); MS (EI, 70 eV): *m/z* (%) = 246 (74, M^+), 127 (100), 105 (97), 86 (48), 57 (60), 50 (34).

2-tert-Butyl-5-phenyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8c**; $C_{14}H_{16}N_4OS$)

Yield: 2.39 g (83%); m.p.: 132–133°C; IR(KBr): $\nu = 1725$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.39 (s, 9H), 5.09 (s, 2H), 7.32–7.444 (s, 5H) ppm; MS (EI, 70 eV): *m/z* (%) = 288 (37, M^+), 169 (42), 154 (11), 119 (16), 105 (100), 104 (36), 86 (61), 57 (23), 56 (11), 50 (13).

2-(4-Methoxy)-phenyl-5-phenyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8d**; $C_{17}H_{14}N_4O_2S$)

Yield: 2.90 g (86%); m.p.: 203–204°C; IR (KBr): $\nu = 1732$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 3.84 (s, 3H), 5.13 (s, 2H), 6.95 (d, 2H, $J = 8.87$ Hz), 7.34–7.47 (m, 5H), 8.12 (d, 2H, $J = 8.87$ Hz); MS (EI, 70 eV): *m/z* (%) = 338 (82, M^+), 219 (17), 177 (19), 161 (26), 133 (100), 105 (43), 104 (28), 90 (16), 57 (16), 50 (12).

2-(4-Ethyl)-phenyl-5-phenyl-5,6,-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8e**; $C_{18}H_{16}N_4OS$)

Yield: 2.72 g (81%); m.p.: 180–181°C; IR (KBr): $\nu = 1735$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.25 (t, 3H), J = 7.6 Hz), 2.69 (q, 2H, $J = 7.6$ Hz), 5.15 (s, 2H), 7.28 (d, 2H, $J = 8.0$ Hz), 7.35–7.48 (m, 5H), 8.11 (d, 2H, $J = 8.0$ Hz); MS (EI, 70 eV): *m/z* (%) = 336 (100, M^+), 175 (10), 159 (30), 131 (20), 105 (46), 86 (17), 57 (69), 50 (15).

2-(2,4-Dichloro)-phenyl-5-phenyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8f**; $C_{16}H_{10}Cl_2N_4OS$)

Yield: 3.19 g (85%); m.p.: 198–199°C; IR (KBr): $\nu = 1732$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 5.20 (s, 2H), 7.34–7.54 (m, 7H), 7.92 (d, 1H) ppm; MS (EI, 70 eV): *m/z* (%) = 376 (71, M^+-1), 378 (57, M^++1), 380 (16, M^++3), 258 (22) 171 (20), 173 (20), 105 (100), 104 (50), 86 (38), 57 (35), 50 (17).

2-(3,5-Dimethyl)-phenyl-5-phenyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8g**; $C_{18}H_{16}N_4OS$)

Yield: 2.75 g (82%); m.p.: 147–148°C; IR (KBr): $\nu = 1720$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 2.36 (s, 6H), 5.15 (m, 2H), 7.09 (s, 1H), 7.37–7.48 (m, 5H), 7.83 (s, 2H) ppm; MS (EI, 70 eV): *m/z* (%) = 336 (60, M^+), 217 (29), 175 (7), 159 (25), 131 (36), 116 (31), 105 (100), 104 (31), 57 (40), 50 (10).

2-tert-Butyl-5-ethyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8h**: $C_{10}H_{16}N_4OS$)

Yield: 1.87 g (78%); m.p.: 125–127°C; IR (KBr): $\nu = 1720$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.32 (t, 3H, $J = 8.2$ Hz), 1.40 (s, 9H), 3.71 (q, 2H, $J = 8.2$ Hz), 4.72 (s, 2H) ppm; MS (EI, 70 eV): *m/z* (%) = 240 (90, M^+), 225 (15), 171(22), 170 (45), 169 (9), 155 (27), 86 (100), 69 (14), 57 (37).

2-(4-Methoxy)-phenyl-5-ethyl-5,6-dihydro-7-thia-1,3,3a,5-tetraaza-inden-4-one (**8i**; $C_{13}H_{14}N_4O_2S$)

Yield: 2.32 g (80%); m.p.: 154–155°C; IR (KBr): $\nu = 1730$ (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, δ, 500 MHz): 1.36 (t, 3H, $J = 8.2$ Hz), 3.76 (q, 2H, $J = 8.2$ Hz), 4.78 (s, 2H), 6.99 (d, 2H, $J = 8.87$ Hz), 8.15 (d, 2H, $J = 8.87$ Hz) ppm; MS (EI, 70 eV): *m/z* (%) = 290 (100, M^+), 177 (15), 161 (19), 133 (62), 86 (5), 57 (20).

Acknowledgements

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