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FLUORENYL PARTICIPATED RING TRANSFORMATION OF URAZOLES TO TRIAZINANEDIONES

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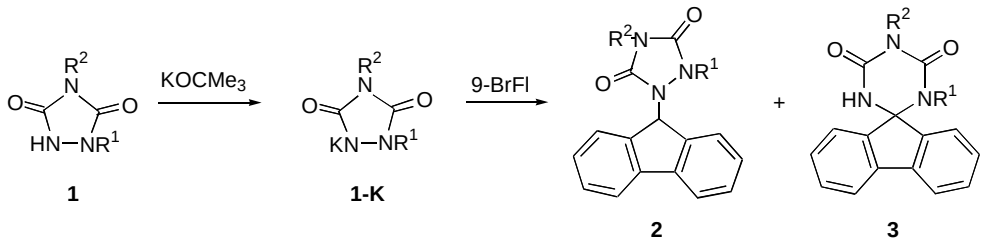
Abstract - Fluorenylation of 1,4-disubstituted urazole (**1**) with 9-bromofluorene affords corresponding fluorenylurazole (**2**) along with the rearrangement product triazinanedione (**3**). The ratio of two products is closely related to the acidity of starting urazole (**1**). Compound (**2**) can be transformed into **3** upon treated with potassium *t*-butoxide. A mechanism involving *N*-acylimine as ring opening intermediate is proposed. The dual roles of urazole anion (**1-K**) are discussed.

Cleavage of N-N bond in urazoles (1,2,4-triazolidine-3,5-diones) is a challenging research area and shows potential synthetic application. Wamhoff and Wald first observed thermal rearrangement of 4-phenyl-1,2,4-triazoline-3,5-dione adducts to spiro-triazinediones in 1977.[1] Later, Sheradsky and Moshenberg reported phototransformation of triazolopyridazinedione to pyrrolotriazinedione.[2] Adam and co-workers discovered an unusual base-catalyzed rearrangement of urazoles and formation of triazinediones in their synthetic utilization of urazoles.[3] Recently, Seguchi and Tanaka developed new methodology using certain active urazoles for the synthesis of some intricate heterocycles,[4] including oxazolidinones, cyanoindoles, and imidazoquinazolinones.

In the course of continuing research aimed at evaluating and understanding of substituent effects on C-H[5] and N-H[6] bond strength, certain fluorenylurazoles (**2**) were targeted as model compounds. The most obvious synthetic approach to **2** appeared to be *via N*-fluorenylation of urazoles (**1**). In this paper, the results and discovery based on above approach are reported.

Reaction of 9-bromofluorene (9-BrFl) with 1,4-dimethyl urazole anion (**1a-K**), generated *in situ* from 1,4-dimethyl urazole (**1a**) and potassium *t*-butoxide in DMSO, gave a mixture of two isomers in

high yield (Scheme 1). As expected, fluorenylurazole (**2a**) was the major product (66%). The minor product (29%) was isolated and characterized as the rearrangement product triazinanedione (**3a**).[7] The reaction was also carried out with a range of other 1,4-disubstituted urazoles (**2b-e**), and the results are summarized in Table 1.



Scheme 1

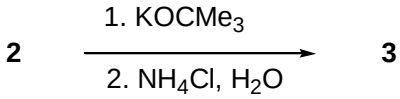
Table 1. Fluorenylation of 1,4-disubstituted urazole (**1**) with 9-bromofluorene *via* Scheme 1

Entry	R^1	R^2	pK_a (**1**)[6]	Ratio (**2**/**3**)[a]	Yield (%) (**2** and **3**)
a	Me	Me	11.4	2.3	95
b	Me	Ph	10.2	3.2	92
c	Ph	Me	9.0	>10	93
d	Ph	Ph	7.9	>10	91
e	4-NO_2Ph	Me	7[b]	>10	88

[a] Evaluated by ^{1}H NMR. [b] Estimated value.

The overall yields for the above reaction were excellent, ranging from 88% to 95%. The ratio of two products formed under these conditions was found to be closely related to the acidities (pK_a) of starting urazoles (**1**). Urazoles (**1**) with higher pK_a value tended to give more rearrangement products (**3**) (lower **2**/**3** ratio). For examples, urazole (**1a**) (pK_a 11.4) and (**1b**) (pK_a 10.2) gave significant amount of rearrangement product (**3a**) and (**3b)** with **2**/**3** ratios of 2.3 and 3.2 respectively. When pK_a value of urazole (**1**) dropped to ≤ 9 as in **1c-e**, substitution product (**2c-e**) became dominant, and the ratios of **2**/**3** were greater than 10.

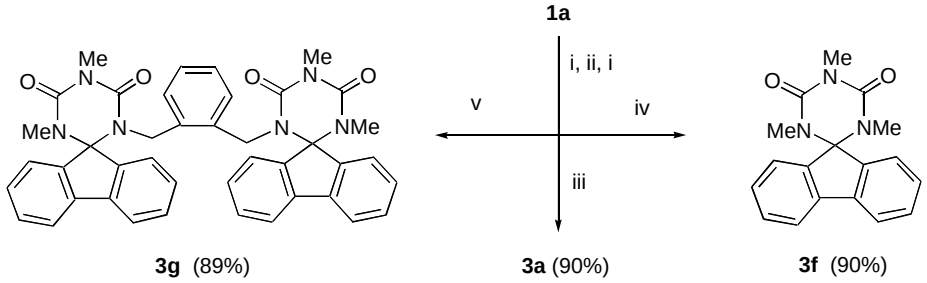
Further treatment of fluorenylurazoles (**2a-e**) with potassium *t*-butoxide in DMSO afforded triazinanediones (**3a-e**) in high yield (82-95%) after acidic aqueous work-up (Scheme 2). The results clearly demonstrate that substitution products (**2a-e**) are precursors of rearrangement products (**3a-e**), and that the ring transformation reaction is a base promoted process.



a. 95%; **b**. 93%; **c**. 94; **d**. 94%; **e**. 82%.

Scheme 2

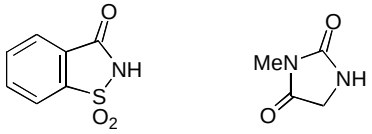
Based on above observation, one-pot transformation was conducted on a selected urazole (**1a**) in four sequential steps (Scheme 3). Potassium salt (**1a-K**) was generated from **1a** (as described early in Scheme 1) and allowed to react with 9-BrFl. The resulting reaction mixture was further treated with potassium *t*-butoxide to form conjugated anion (**3a-K**) of triazinanedione (**3a**). Anion (**3a-K**) was subsequently quenched with different electrophiles, namely, NH_4Cl/H_2O, MeI, and α,α'-dichloro-*o*-xylene, and the corresponding rearrangement products (**3a**, **3f**, and **3g**) were obtained in excellent yields. The structure of **3g** was conformed by X-Ray analysis.[8]



i. $KOCMe_3$. ii. 9-BrFl. iii. NH_4Cl, H_2O. iv. MeI. v. o-$(ClCH_2)_2C_6H_4$.

Scheme 3

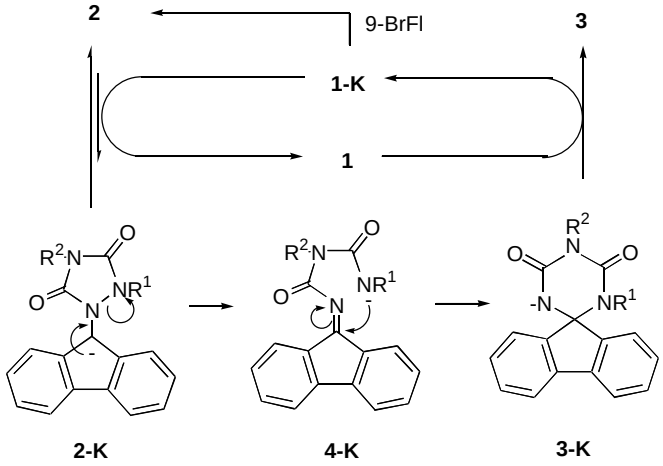
The pK_a window for the above substitution and rearrangement reaction was explored by examining the reactivity of two selected substrates (Figure 1) with 9-BrFl and fluorenylurazole (**2d**).[9] These two substrates were saccharin with pK_a of 4.0[10] and 3-methylhydantoin with pK_a of 19.0.[11] Reaction results showed that saccharin anion was neither nucleophilic enough to undergo substitution reaction with 9-BrFl, nor basic enough to promote ring expansion of fluorenylurazole (**2d**). 3-Methylhydantoin anion, on the other hand, behaved like potassium *t*-butoxide (for *t*-BuOH, pK_a = 32.2[10]). It converted 9-BrFl to bifluorenylidine[12] instead of substitution product, and transformed fluorenylurazole (**2d**) to corresponding triazinanedione (**3d**).



pK_a 4.0 pK_a 19.0

Figure 1

A possible mechanism for the formation of triazinanedione (**3**) in the reaction of urazole anion (**1-K**) with 9-BrFl is shown in Scheme 4. Fluorenylurazole (**2**), the initial product from the reaction, can undergo proton exchange reaction with unreacted **1-K** to generate fluorenyl anion (**2-K**) and urazole (**1**). Anion (**2-K**) then promotes the N-N bond cleavage reaction to give ring opening *N*-acylimine anion (**4-K**) as a reactive intermediate.[13] Subsequent ring closure of **4-K** *via* intramolecular Michael type addition generates triazinanedione anion (**3-K**). Anion (**3-K**) is much more basic than anion (**1-K**).[14] Therefore proton transfer occurs from urazole (**1**) to form triazinanedione (**3**), and regenerates urazole anion (**1-K**). This cycle is continued until anion (**1-K**) is consumed.



Scheme 4

Urazole anion (**1-K**) played two roles in the reaction. It acted as a nucleophile reacting with 9-BrFl to form fluorenylurazole (**2**). It also served as a weak base deprotonating **2** to **2-K** and initializing the conversion process to **3**. These two functions competed each other. Decreasing acidity of urozole (**1**) (increasing pK_a) favors deprotonation of **2** to **2-K**, which results in the formation of rearrangement product (**3**) (decreasing of **2**/**3** ratio). When pK_a of urazole **1** ≤ 9, the deprotonation of **2** becomes less favored, the substitution process consumes more urazole anion (**1-K**) to form **2** and **2**/**3** ratio is increased. This interpretation correctly reflects the correlation between pK_a values and **2**/**3** ratios in Table 1. Furthermore, when fluorenylurazole (**2**) is treated with the strong base potassium *t*-butoxide (as in Scheme 2), it is fully deprotonated to **2-K**, which rearranges to anion (**3-K**). Acidic aqueous work-up is needed to protonate **3-K** to **3**.

In summary, an efficient ring transformation of some 1,4-disubstituted urazoles through a stepwise process or one-pot process was described. The mechanism and the effect of pK_a on the reaction were discussed.

EXPERIMENTAL

All melting point were measured on a Thomas-Hoover Unimelt capillary melting point apparatus and uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR model 1605 and samples were prepared as Nujol mulls. ^{1}H NMR and ^{13}C NMR were determined on a Varian VXR-300 Spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc. Norcross, GA, USA.

General procedure for the fluorenylation of 1,4-disubstituted urazole (1). To a solution of 1,4-disubstituted urazole (**1**) (3.0 mmol) in DMSO (4 mL) was added potassium *t*-butoxide (0.35 g, 3.0 mmol). After stirring for 40 min under N_2 at rt, 9-bromofluorene (0.75 g, 3.0 mmol) in DMSO (3 mL) was then added. The resulting mixture was stirred at same condition for another 12 h before being quenched with ice water (20 mL). The solid was collected and washed with water. Fluorenylurazole (**2**) and triazinanedione (**3**) were separated by chromatography on silica gel (30-60% ethyl acetate-hexane). Fluorenylurazole (**2**) was recrystalized from ethanol-acetone.

General procedure for the conversion of fluorenylurazole (2) to triazinanedione (3). A solution of fluorenylurazole (**2**) (0.50 mmol) in DMSO (2 mL) was treated with potassium *t*-butoxide (0.065 g, 0.55 mmol) at rt. The resulting solution was stirred under N_2 for 3 h, then quenched with NH_4Cl/H_2O. The solid was filtered and washed with water. Triazinanedione (**3**) was purified by recrystalization from ethanol-chloroform.

One-pot preparation of triazinanedione (3a). To a solution of 1,4-dimethylurazole (**1a**) (0.12 g, 1.0 mmol) in DMSO (1.5 mL) was added potassium *t*-butoxide (0.12 g, 1.0 mmol). After stirring for 40 min under N_2 at rt, 9-bromofluorene (0.25 g, 1.0 mmol) in DMSO (1.5 mL) was then added. The resulting mixture was stirred at same condition for another 12 h before being further treated with potassium *t*-butoxide (0.13 g, 1.1 mmol) for 3 more hours. The resulting **3a-K** solution was quenched with ice-water to give **3a** (as described above).

One-pot preparation of triazinanedione (3f). To the triazinanedione anion solution (**3a-K**) (1.0 mmol scale, as described before) was added iodomethane (2 mL). The resulting solution was stirred for 20 min at rt, then added to ice-water (20 mL). The aqueous solution was extracted with ether (3×7 mL), dried ($MgSO_4$), and evaporated to dryness. Product (**3f**) was further purified by recrystalization from ethanol.

One-pot preparation of triazinanedione (3g). To the triazinanedione anion solution (**3a-K**) (1.0 mmol scale, as described before) was added a DMSO solution (1.5 mL) of α,α'-dichloro-*o*-xylene (0.087 g, 0.50 mmol). The white solid product was collected from the reaction and washed with acetone. Product (**3g**) was recrystalized from acetone-chloroform.

Fluorenylurazole (2a): mp 157-158 °C; IR 1778, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.75-7.30 (m, 8H), 6.38 (s, 1H), 3.22 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 155.9, 154.6, 140.5, 140.4, 129.5, 127.9, 125.0,

120.5, 61.5, 33.9, 25.9. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.64; H, 5.20; N, 14.41.

Fluorenylurazole (2b): mp 163-164 °C; IR 1766, 1714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78-7.34 (m, 13H), 6.49 (s, 1H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.7, 152.9, 140.5, 140.3, 131.6, 129.6, 129.2, 128.3, 128.0, 125.5, 125.0, 120.6, 61.8, 33.9. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.27; H, 4.71; N, 11.93.

Fluorenylurazole (2c): mp 168-169 °C; IR 1778, 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62-6.86 (m, 18H), 6.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 155.0, 151.7, 141.0, 139.9, 135.1, 131.4, 129.2, 128.5, 125.4, 128.2, 127.6, 126.2, 125.6, 125.0, 120.1, 63.1. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.36; H, 4.72; N, 11.96.

Fluorenylurazole (2d): mp 158-159 °C; IR 1777, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50-6.79 (m, 13H), 6.13 (s, 1H), 1.60 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 156.1, 153.2, 140.8, 140.0, 135.3, 129.1, 128.5, 128.0, 127.5, 126.0, 124.9, 120.0, 62.7, 25.9. Anal. Calcd for $C_{27}H_{19}N_3O_2$: C, 77.68; H, 4.59; N, 10.07. Found: C, 77.75; H, 4.65; N, 9.98.

Fluorenylurazole (2e): mp 222-223 °C; IR 1789, 1726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.85-6.90 (m, 12H), 6.18 (s, 1H),3.25 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 157.1, 156.6, 152.2, 145.8, 140.9, 139.4, 129.6, 127.8, 125.2, 124.7, 123.6, 120.2, 64.0, 26.2. Anal. Calcd for $C_{22}H_{16}N_4O_4$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.68; H, 3.87; N, 13.97.

Triazinanedione (3a): mp 288-289 °C; IR 3380, 1708, 1664 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.64-7.31 (m, 8H), 5.50 (s, 1H), 3.34 (s, 3H), 2.44 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.5, 152.7, 143.6, 139.1, 131.0, 129.1, 124.1, 120.5, 80.6, 29.8, 28.1. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.55; H, 5.15; N, 14.23.

Triazinanedione (3b): mp 278-279 °C; IR 3213, 1714, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68-7.38 (m, 13H), 5.57 (s, 1H), 2.50 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.1, 152.2, 143.5, 139.2, 135.1, 131.1, 129.2, 129.1, 129.0, 128.9, 124.1, 120.7, 77.9, 29.9. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.20; H, 4.66; N, 11.73.

Triazinanedione (3c): mp 260-261 °C; IR 3272, 1719, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87-6.68 (m, 18H), 5.77 (s, 1H) ^{13}C NMR ($CDCl_3$) δ 152.8, 150.0, 143.9, 139.3, 136.6, 134.9, 134.8, 131.0, 129.0, 128.9, 128.5, 128.4, 128.0, 124.6, 120.5, 78.5. Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.32; H, 4.68; N, 11.92.

Triazinanedione (3d): mp 298-299 °C; IR 3202, 1714, 1674 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.66-6.61 (m, 13H), 5.67 (s, 1H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.4, 153.3, 144.0, 129.2, 136.6, 130.8, 129.0,

128.8, 128.4, 127.9, 124.6, 120.4, 78.2, 28.2. Anal. Calcd for $C_{27}H_{19}N_3O_2$: C, 77.68; H, 4.59; N, 10.07. Found: C, 77.75; H, 4.58; N, 10.14.

Triazinanedione 3e: mp 271-272 °C; IR 3032, 1715, 1669 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.86-6.78 (m, 12H), 5.79 (s, 1H), 3.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 152.8, 151.5, 146.7, 143.3, 142.9, 139.1, 131.4, 129.7, 129.2, 124.4, 123.7, 120.8, 105.6, 78.1, 28.3. Anal. Calcd for $C_{22}H_{16}N_4O_4$: C, 66.00; H, 4.03; N, 13.99. Found: C, 65.98; H, 3.85; N, 13.62.

Triazinanedione (3f): mp 194-195 °C; IR 1692, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33-7.80 (m, 8H), 3.40 (s, 3H), 2.40 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.7, 153.0, 142.3, 139.8, 130.9, 129.2, 124.1, 120.5, 105.6, 30.3, 28.7. Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 69.98; H, 5.47; N, 13.73.

Triazinanedione (3g): mp 303-305 °C; IR 1706, 1666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.52-7.50 (m, 20H), 3.64 (s, 4H), 3.30 (s, 6H), 2.27 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 153.7, 153.3, 141.4, 139.8, 134.9, 130.7, 128.4, 127.1, 126.3, 124.5, 120.3, 82.4, 44.7, 30.2, 28.9. Anal. Calcd for $C_{42}H_{36}N_6O_4$: C, 73.24; H, 5.27; N, 12.20. Found: C, 72.95; H, 5.18; N, 12.22.

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7. Triazinanedione (**3**) has much higher mp than fluorenylurazole (**2**), indicating the intermolecular N-H··· O=C hydrogen bonding in the solid state of **3**. The IR spectrum of compound (**3**) also showed N-H stretch (3202-3380 cm^{-1}). ^1H NMR showed that, N-H signal (5.50-5.79 ppm) in **3** decreased

progressively during D/H exchange experiment. Triazinanedione structure was further confirmed by X-Ray analysis.[8]

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14. The pK_a of 3-phenyl-1,3,5-triazinane-2,4-dione in DMSO was determined to be 17.8.