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Acylimine mediated N–N bond cleavage of pyrazolidinediones and subsequent conversion to dihydropyrimidinediones and malonamides

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Abstract—Acylimines **3** were identified as intermediates in the fluorenyl assisted N–N bond cleavage of pyrazolidinediones **1**. Subsequent conversion of **3** to dihydropyrimidinediones **4** and malonamides **7**–**10** is described. © 2000 Published by Elsevier Science Ltd.

Reductive cleavage of the N–N bond under strongly reducing conditions, e.g. metal (Li, Na) in ammonia, Raney Nickel, or SmI_2, can provide an efficient synthetic route to amino/acylamino and diamino derivatives.1 This type of functionality can also be accessed by base promoted N–N bond cleavage of diazetidinones and acyl hydrazines.2 Acylimines, on the other hand, are valuable, reactive reagents in the organic synthesis[3] which have served as building blocks for various amino acid derivatives,[4] including the Taxol A-ring side-chain,[5] and β-amido aldehydes.[6] Acylimines have also been invoked as intermediates in the ring transformation of diazetidinones,7 indazolones,[8] and urazoles.[9] However, there is no direct empirical evidence for their formation during these reactions.

Previously, we reported an efficient insertion of fluorenylene into urazoles to provide the corresponding triazinanediones.[10] In this letter, we describe the reaction of 9-bromofluorene with pyrazolidinediones leading to the initial formation of stable acylimine intermediates which can be converted into cyclic insertion products or to acyclic acylamino/amino derivatives, depending on the reaction conditions.

In an initial experiment, reaction of 9-bromofluorene (9-BrFl) with the potassium salt of **1a** (**1a**–**K**), generated in situ from 4,4-diethyl-1-methylpyrazolidine-3,5-dione and potassium *t*-butoxide ($KOCMe_3$), provided three products (Scheme 1). These products were separated and characterized as the substitution product, fluorenyl pyrazolidinedione **2a** (5%), the ring opening product, acylimine **3a** (65%) and the insertion product pyrimidinedione **4a** (12%), respectively.[11,12]

The isolation of acylimine **3a** is significant, in that, to our knowledge, this is the first example of a stable acylimine being generated from N–N bond cleavage of an acyl hydrazine. Our mechanistic proposal for the formation of acylimine **3a** is also illustrated in Scheme 1. Compound **2a**, the initial product from the reaction, undergoes proton exchange with unreacted anion **1a**–**K** to generate fluorenyl anion **2a**–**K** and pyrazolidinedione **1a**. Anion **2a**–**K** then promotes the N–N bond cleavage to give acylimine anion **3a**–**K**. Proton exchange from **1a** to **3a**–**K** forms acylimine **3a**, and regenerates anion **1a**–**K**. The isolation of the insertion product **4a** as a minor component of the reaction mixture reflects a relatively unfavorable competition reaction, in which the acylimine anion **3a**–**K** cyclizes to anion **4a**–**K**, and then is protonated by **1a**.

Schemes 2–6 illustrate some simple manipulations of this basic reaction system which provide a variety of products. When pyrazolidinedione **1b** (Scheme 2) was first treated with $KOCMe_3$, and then allowed to react with 9-BrFl and the crude products further treated with

Keywords: acylimine; cleavage reactions; cyclization; fluorenes; ring transformations.

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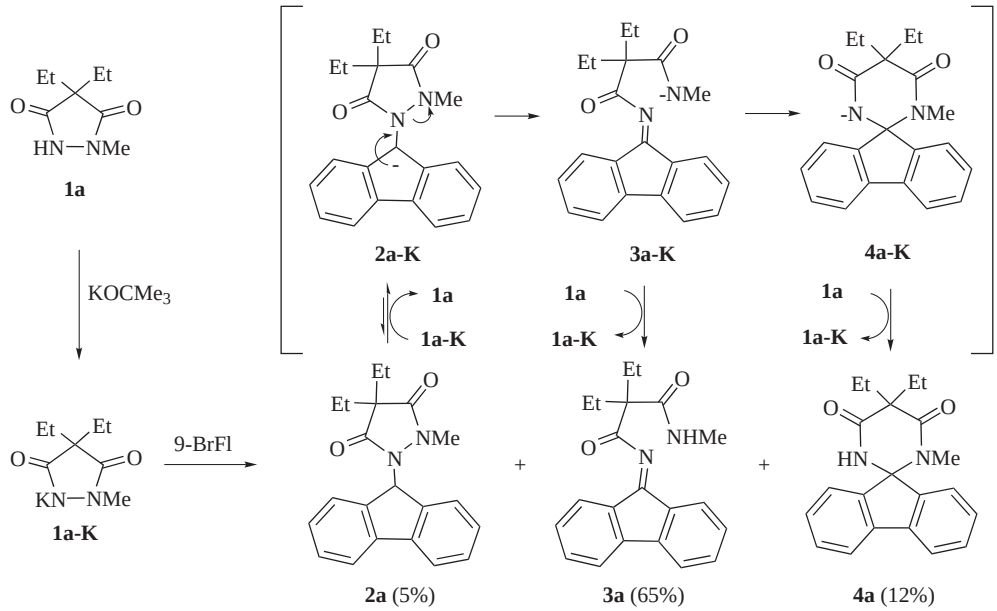
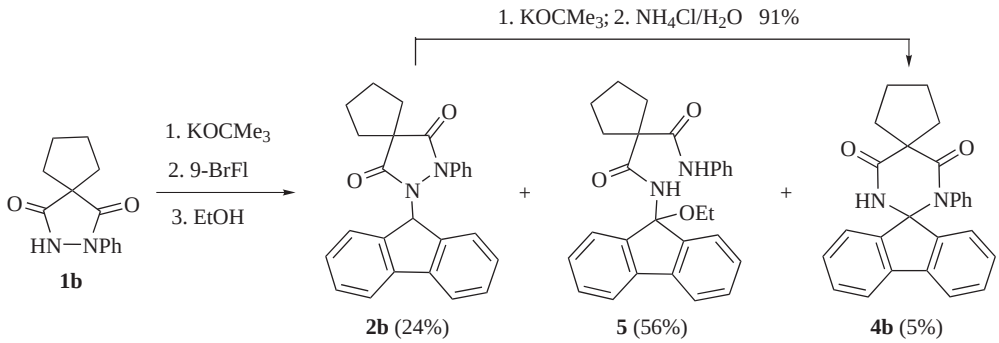
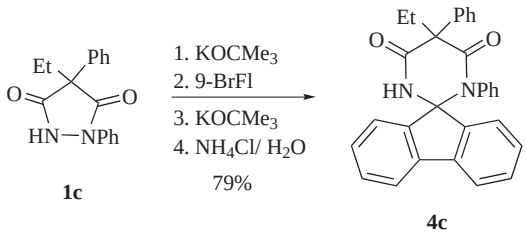


Scheme 1.



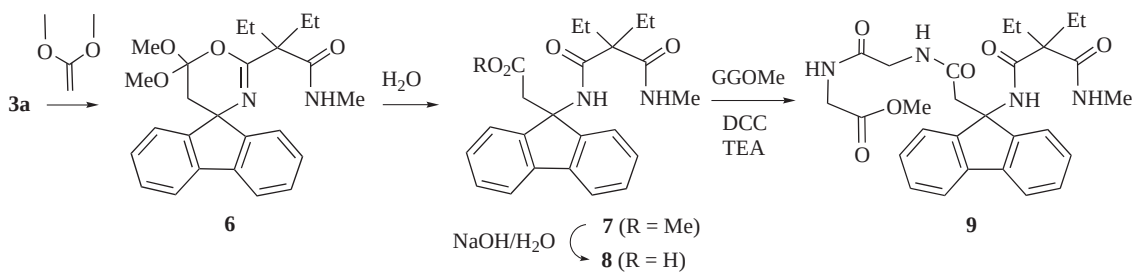
Scheme 2.



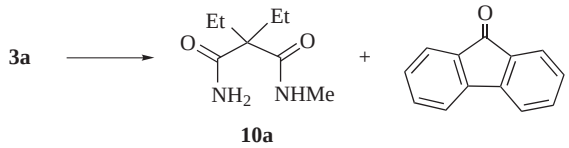
Scheme 3.

ethanol, malonamide **5**, the addition product of EtOH to the corresponding acylimine, was the major product (56%), along with substitution product **2b** (24%) and insertion product **4b** (5%).

However, when **2b** was subsequently treated with $KOCMe_3$ and the reaction quenched with aqueous NH_4Cl, **4b** was obtained in high yield (91%), presumably, via the process of deprotonation, cleavage, cyclization, and protonation, as discussed above.



Scheme 4.



10a

Scheme 5.

One-pot insertion of fluorenylene into the N–N bond is outlined in Scheme 3. Pyrazolidinedione **1c** was first treated with $KOCMe_3$ and then allowed to react with 9-BrFl. The resulting reaction mixture was further treated with $KOCMe_3$ before being quenched with NH_4Cl/H_2O to give, on isolation, the insertion product **4c** (79%).

Cycloaddition of acylimine **3a** with 1,1-dimethoxyethylene[3] (Scheme 4) produced dihydrooxazine **6**, which was hydrolyzed under mild conditions to ester **7**. Further hydrolysis of **7** gave acid **8**. Coupling of **8** with glycylglycine methyl ester (GGOMe) yielded the novel peptide product **9**.

Acylimine **3a** is sensitive to moisture and is hydrolyzed to malonamide **10a** and 9-fluorenone upon standing (Scheme 5). This observation led us to explore the practicality of an one-pot approach to 2,2,*N*-trisubstituted malonamides (Scheme 6). 1,5,5-Trisubstituted pyrazolidinediones (**1a**–**d**) were treated with $KOCMe_3$, and allowed to react with 9-BrFl. The resulting reaction mixtures were then simply exposed to moisture. Gratifyingly, 2,2,*N*-trisubstituted malonamides (**10a**–**d**) were obtained in good yields (59–65%).[13] This overall process can be considered as reductive cleavage of N–N bond in pyrazolidinedione **1** with the reducing agent 9-BrFl being oxidized to 9-fluorenone.[14]

In conclusion, acylimines have been isolated for the first time as products from N–N bond cleavage of pyrazolidinediones. Further useful transformations of these intermediates to dihydropyrimidinediones and 2,2,*N*-trisubstituted malonamides have been developed.

Acknowledgements

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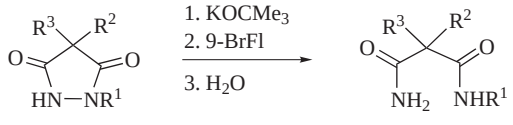

1 10

a. R^1 = Me, $R^2 = R^3$ = Et	65%
b. R^1 = Ph, $R^2 = R^3 = -(CH_2)_4-$	59%
c. $R^1 = R^2$ = Ph, R^3 = Et	58%
d. $R^1 = R^2 = R^3$ = Me	61%

Scheme 6.

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11. **2a**: mp 138–139°C; IR (KBr) 1706, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29–7.70 (m, 8H), 6.82 (s, 1H), 3.38 (s, 3H), 1.68 (m, 4H), 0.83 (t, $J = 7.5$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 174.0, 172.8, 141.8, 141.0, 129.8, 127.9, 55.3, 31.0, 27.4, 8.9. Anal. calcd for $C_{21}H_{22}N_2O_2$: C,75.42; H, 6.63; N, 8.38. Found: C, 75.08; H, 6.65; N, 8.42. **3a**: IR (KBr) 3366, 1713, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.69 (m, 9H), 2.90 (d, $J = 4.5$ Hz, 3H), 2.05 (m, 4H), 0.93 (t, $J = 7.5$ Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 189.3, 171.7, 143.3, 134.7, 133.6, 128.5, 125.6, 120.4, 105.6, 61.4, 28.9, 26.4, 9.7. EI MS *m/e* 334. **4a**: mp 300–301°C; IR (KBr) 3201, 1670, 1626 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.68 (m, 8H), 6.20 (s, 1H), 2.46 (s, 3H), 2.11 (m, 4H), 1.13 (t, $J = 7.5$

Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 170.9, 170.3, 144.1, 139.2, 130.9, 129.2, 123.9, 120.7, 79.7, 55.5, 31.9, 29.3, 11.0. Anal. calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.34; H, 6.62; N, 8.38.

12. For X-ray crystal structure of **4a**, see: Gong, Y.; Robinson, P. D.; Bausch, M. J. *Acta Crystallogr*., Sect. C **1996**, *52*, 2081–2084.
13. Preparation of tetrasubstituted malonamides from decarbonylation of barbituric acids was reported recently: Jursic, B. S. *Tetrahedron Lett*. **2000**, *41*, 5325–5328.
14. With fluorenyl pyrazolidinediones (**2**) and dihydropyrimidinediones (**4**) as the by-products.