JOC Note

# Facile Synthesis of 4-Alkyl (and Aryl)-2-aryl-6-diazo-4*H*-thieno[3,2-*b*]pyridine-5,7-diones

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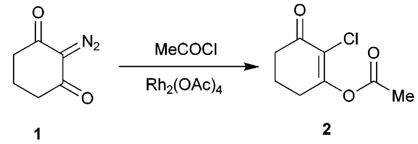
**Abstract:** Treatment of 3-{3-alkyl (and aryl)amino-5-arylthieno-2-yl}-2-diazo-3-oxopropanoates **8** with TMSOTf (3 equiv) in the presence of $Et_3N$ (6 equiv) in $CH_2Cl_2$ for 1 h at room temperature afforded 4-alkyl (and aryl)-2-aryl-6-diazo-4*H*-thieno[3,2-*b*]pyridine-5,7-diones **14** in excellent yields. On heating of **14** in the presence of a catalytic amount of $Rh_2(CF_3CF_2CF_2CO_2)_4$ in PhH for 4−10 h at reflux, corresponding ring contraction products, 4-alkyl (and aryl)-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-5-ones **16**, were produced in good to excellent yields.

2-Diazocyclohexane-1,3-dione and diazoquinolinedione derivatives are an important class of organic compounds. The former are utilized as intermediates for the synthesis of $\beta$-substituted $\alpha$-chloroenones that are used as valuable intermediates in the synthesis of $\alpha$-carbon-substituted enones[1] and biologically active natural products.[2] For example, treatment of 2-diazocyclohexane-1,3-dione **1** with acetyl chloride at room temperature for 3 h gave 3-acetoxy-2-chlorocyclohex-2-enone **2** in 81% yield[3] (Scheme 1).

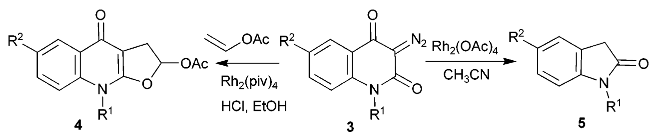
The latter are useful for the synthesis of biologically active compounds. For example, *N*-alkyldiazoquinolinedione **3** undergoes cyclization with vinyl acetate in the presence of $Rh_2(piv)_4$ catalyst in acidic EtOH to give 2-acetoxy-9-alkyl-2,3-dihydrofuro[2,3-*b*]quinoline-4-one **4**[4] (Scheme 2), which can be further converted to naturally occurring alkaloids.

In addition, rhodium(II)-catalyzed reactions of **3** in refluxing $CH_3CN$ gave oxindoles **5**[5,6] (Scheme 2), which are valuable synthetic intermediates of natural and pharmaceutical reagents. Compounds **1** and **3** were readily prepared by the diazo transfer reactions of the corresponding 1,3-diones with mesyl azide according to

**SCHEME 1**




**SCHEME 2**

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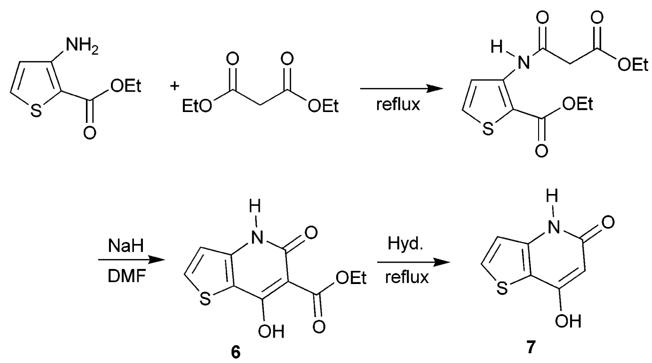


Taber's method.[7] Quinolinediones, precursors of **3**, are either commercially available or can be prepared by cyclizing the corresponding anthranilic acids with acetic anhydride in acetic acid.[8] Surprisingly, 6-diazo-4*H*-thieno-[3,2-*b*]pyridine-5,7-diones or 6-diazo-4*H*-furo[3,2-*b*]pyridine-5,7-diones, analogous to compounds **3**, have not been reported.

A search of the literature revealed that there is one report[9] describing the synthesis of 7-hydroxy-4*H*-thieno-[3,2-*b*]pyridine-5-one **7** by hydrolysis, followed by decarboxylation of 6-ethoxycarbonyl-7-hydroxy-4*H*- thieno[3,2-*b*]pyridin-5-one **6**, prepared starting from ethyl 3-aminothiophene-2-carboxylate and diethyl malonate in two steps (Scheme 3). However, the method is of limited usefulness due to difficulty with accessing the introduction of aryl groups at the nitrogen atom of the pyridine moiety as well as the inaccessibility of the starting materials, i.e., 3-aminothiophene-2-carboxylate with diverse substituents at the 5-position.

Accordingly, it may be worthwhile to explore the synthetic method of the foregoing unexplored fused pyridine-5,7-diones, whose diazo compounds would be expected to comprise a promising starting material for the synthesis of novel bioactive compounds.

Recently, we reported a synthesis of a mixture of 5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-5-one and the correspond-

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(1) Lee, Y. R.; Jung, Y. S. *J. Chem. Soc., Chem. Commun.* **1998**, 2621−2622 and references cited therein.
(2) (a) Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014−11015. (b) Johnson, C. R.; Harikrishnan; Golebiowski, A. *Tetrahedron Lett.* **1994**, *35*, 7735−7738.
(3) (a) Alonso, M. E.; Chitty A. W. *Tetrahedron Lett.* **1981**, *22*, 4181−4184. (b) Alonso, M. E.; Garcia, M. C.; Chitty, A. W. *J. Org. Chem.* **1985**, *50*, 3445−3449.
(4) Pirrung, M. C.; Blume, F. *J. Org. Chem.* **1999**, *64*, 3642−3649.
(5) Lee, Y. R.; Jung, Y. S.; Kim, B. S. *Tetrahedron Lett.* **1999**, *40*, 8219−8221.
(6) (a) Lakahmaiah, G.; Kawabata, T.; Shang, M.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699−1704. (b) van Henegouwen, W. G. B.; Hiemstra, H. *J. Org. Chem.* **1997**, *62*, 8862−8867. (c) Miah, S.; Moody, C. J.; Richards, I. C.; Slawin, A. M. Z. *J. Chem. Soc., Perkin Trans. 1.* **1997**, 2405−2412.
(7) Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. *J. Org. Chem.* **1986**, *51*, 4077−4078.
(8) (a) Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Spice, B. A. *J. Med. Chem.* **1975**, *18*, 726−732. (b) Lutz, R. E.; Codington, J. F.; Rowlett, R. J.; Deint, A. J.; Bailey, P. S. *J. Am. Chem. Soc.* **1946**, *68*, 1810−1812.
(9) Baker, J. M.; Huddleston, P. R.; Chadwick, N.; Keenan, G. J. *J. Chem. Res., Synop.* **1980**, 6−7.

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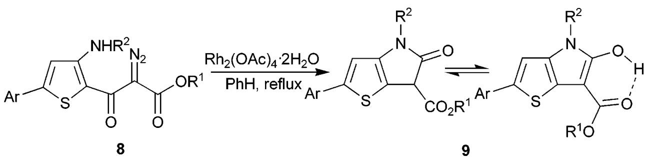
**SCHEME 4**



**SCHEME 5**

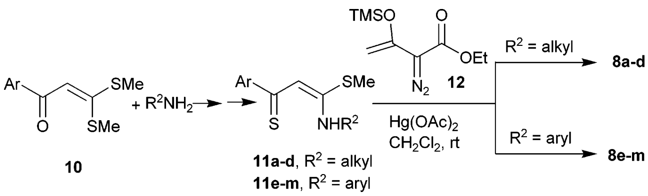


**TABLE 1. Yields of Compounds 11 and 8**

| Ar | $R^2$ | compd | % yield[a] | compd | % yield[a] |
|---|---|---|---|---|---|
| Ph | Me | **11a** | 87 | **8a** | 91 |
| Ph | Et | **11b** | 80 | **8b** | 71 |
| Ph | *i*-Pr | **11c** | 72 | **8c** | 52 |
| 4-$MeC_6H_4$ | Me | **11d** | 66 | **8d** | 77 |
| Ph | 4-$MeOC_6H_4$ | **11e** | 78 | **8e** | 80 |
| Ph | 2-$MeC_6H_4$ | **11f** | 74 | **8f** | 83 |
| Ph | 4-$ClC_6H_4$ | **11g** | 71 | **8g** | 87 |
| Ph | 2-$NCC_6H_4$ | **11h** | 64 | **8h** | 38 |
| 4-$MeOC_6H_4$ | 4-$MeOC_6H_4$ | **11i** | 69 | **8i** | 88 |
| 4-$MeOC_6H_4$ | 4-$BrC_6H_4$ | **11j** | 53 | **8j** | 53 |
| 4-$MeOC_6H_4$ | 4-$NCC_6H_4$ | **11k** | 72 | **8k** | 57 |
| 4-$BrC_6H_4$ | Ph | **11l** | 68 | **8l** | 77 |
| 4-$BrC_6H_4$ | 4-$MeOC_6H_4$ | **11m** | 69 | **8m** | 88 |

[a] Isolated yields.

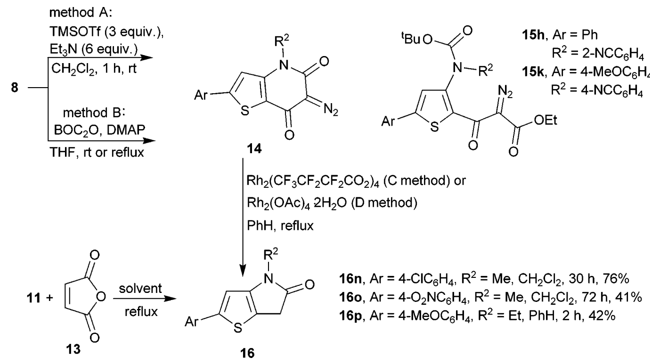
ing enols **9** from the reactions of 3-(3-alkylamino-5-arylthieno-2-yl)-2-diazo-3-oxopropanoates **8** ($R^1 = R^2 =$ alkyl) with a catalytic amount of $Rh_2(OAc)_4{\cdot}2H_2O$ in benzene at reflux[10] (Scheme 4).

Synthesis of compounds **8e**–**m** was achieved by treatment of thioaroylketene *S*,*N*-acetals **11e**–**m**, prepared by the reactions of aroylketene *S*,*S*-acetals **10** with arylamines in the presence of $BF_3{\cdot}OEt$,[11] followed by treatment of Lawesson's reagent,[12] with 2-diazo-3-trimethylsilyloxy-3-butenoate **12** in the presence of $Hg(OAc)_2$ (Scheme 5). Yields of compounds **8** and **11** are summarized in Table 1.

We found that compounds **8** were excellent starting materials for the synthesis of title compounds **14**, which were prepared by the reactions of compounds **8** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) (3 equiv) in the presence of $Et_3N$ (6 equiv) in $CH_2Cl_2$ for 1 h at room temperature in excellent yields (Scheme 6, method A). Yields of **14** are summarized in Table 2.

It is interesting to note that dihydro- and tetrahydrothieno[3,2-*b*]pyridines are seldom reported[13] despite ample examples of thieno[3,2-*b*]pyridine-5-one derivatives that are biologically important.[14] However, no diazothieno[3,2-*b*]pyridinediones whatsoever have been reported.

**SCHEME 6**



Alternatively, compounds **14** could be prepared utilizing di-*tert*-butoxycarbonate ($BOC_2O$) and *N*,*N*-(dimethylamino)pyridine (DMAP)[15] (method B). Their yields are listed in Table 2.

Table 2 shows that very high yields of **14** were obtained in 1 h reactions regardless of whether $R^2$ is alkyl or aryl group when TMSOTf and $Et_3N$ were used, whereas low yields of **14a**–**d** were obtained in the cases of $R^2 =$ alkyl groups when $BOC_2O$ and DMAP were used. In contrast, yields of **14** were comparable or inferior to those obtained under conditions involving TMSOTf in the cases where $R^2 =$ aryl groups. One crucial drawback of the reactions involving $BOC_2O$ and DMAP was the recovery of a considerable amount of **8** in most of the reactions. In addition, the reaction times were variable depending on the properties of $R^2$. It appeared that the cyclization reactions proceeded slowly when $R^2$ was an aryl group having an electron-donating group such as methoxy (**14e** and **14i**) and alkyl groups (**14a**–**d**). In particular, it took 10 and 24 h, respectively, when Ar = Ph, $R^2$ = Me (**14a**) and Ar = 4-$MeC_6H_4$, $R^2$ = Me (**14d**). When $R^2$ = 2-$MeC_6H_4$ (**14f**), it took 15 h presumably due to the steric hindrance arising from the *o*-methyl group. It may be worthwhile to mention that the reactions of **8h** and **8k** occurred smoothly at room temperature for a shorter time (0.5 h) to give the corresponding cyclized product **14h** and **14k**, along with *t*-BOC-protected starting materials **15h** (27%) and **15k** (17%), respectively, in addition to the starting material. The role of $BOC_2O$ and DMAP in the cyclization of **8** to give **14** is uncertain. Treatment of **15h**, presumably formed via 1-*tert*-butoxycarbonyl-4-dimethylaminopyridinium *tert*-butyl carbonate,[16] with a mixture of $BOC_2O$ and DMAP for 24 h at reflux under the same foregoing conditions, did not give **14h**. Only **15h** was quantitatively recovered. The result suggests that *N*-BOC-protected **8** may not be a reactive intermediate leading to **14**. In contrast, treatment of **8a**, **8c**, **8e**, and **8g** with *tert*-BuOK (0.2 equiv) in THF at room temperature gave **14a** (93%), **14c** (78%), **14e** (95%), and **14g**

(10) Lee, D. J.; Kim, K.; Park, Y. J. *Org. Lett.* **2002**, *4*, 873–876.
(11) Kohra, S.; Turuya, S.; Kimura, M.; Ogata, K. *Chem. Pharm. Bull.* **1993**, *41*, 1293–1296.
(12) Huang, Z.-t.; Liu, Z.-r. *Synth. Commun.* **1989**, *19*, 943–958.
(13) Brugier, D.; Oututquin, F.; Paulmier, C. *J. Chem. Soc., Perkin Trans. 1.* **2001**, 37–43.

(14) (a) Suzuki, F.; Miwa, Y.; Hayashi, H.; Ishii, A.; Ichikawa, S.; Miki, I. Eur. Pat. Appl. CODEN; EPXXDW EP 503822 A1 19920916, 1992. (b) Luo, J. K.; Castle, R. N. *J. Heterocycl. Chem.* **1991**, *28*, 205–208. (c) Malicorne, G.; Bompart, J.; Giral, L.; Despaux, E. *Eur. J. Org. Chem.* **1991**, *26*, 3–11. (d) Davies, R. V. Eur. Pat. Appl. CODEN; EPXXDW EP 269295 A1 199880601, 1998.
(15) Koskinen, A. M. P.; Pihko, P. M. *Tetrahedron Lett.* **1994**, *35*, 7417–7420.
(16) (a) Knölker, H.-J.; Braxmeier, T.; Schlechtingen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 7–2500. (b) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494–501.

**TABLE 2. Yields of Compounds 14 and 16**

| | | method A | method B | | | method C | | method D | |
|---|---|---|---|---|---|---|---|---|---|
| reactant | product | % yield[a] | % yield[a] | time, h | product | % yield[a] | time, h | % yield[a] | time, h |
| **8a** | **14a** | 91 | 54 (40)[c] | 10 | **16a** | 77 | 6 | 72 | 3 |
| **8b** | **14b** | 63 | 0 (94)[c] | 24 | **16b** | 79 | 7 | 73 | 5 |
| **8c** | **14c** | 57 | 0 (95)[c] | 24 | **16c** | 70 | 7 | 44 | 5 |
| **8d** | **14d** | 96 | 49 (44)[c] | 24 | **16d** | 88 | 4 | 47 | 4 |
| **8e** | **14e** | 90 | 93 | 1 | **16e** | 87 | 5 | 79 | 6 |
| **8f** | **14f** | 95 | 64 (30)[c] | 15 | **16f** | 92 | 8 | 28 | 4 |
| **8g** | **14g** | b | 93 | 1 | **16g** | 96 | 4 | 34 | 5 |
| **8h** | **14h** | 91 | 64 (27)[d] | 0.5[e] | **16h** | 95 | 6 | 33 | 3 |
| **8i** | **14i** | 87 | 80 (19)[c] | 2 | **16i** | 99 | 5 | 35 | 4 |
| **8j** | **14j** | 94 | 95 | 0.5 | **16j** | 62 | 5 | 45 | 3 |
| **8k** | **14k** | b | 81 (17)[d] | 0.5[e] | **16k** | 71 | 10 | 65 | 3 |
| **8l** | **14l** | 89 | 95 | 0.5 | **16l** | 87 | 8 | 74 | 2 |
| **8m** | **14m** | 95 | 96 | 0.5 | **16m** | 92 | 7 | 59 | 2 |

[a] Isolated yields. [b] Reactions were not carried out. [c] Yields of recovered **8**. [d] Yields of compounds **15h** and **15k**. [e] Reactions were carried out at room temperature.

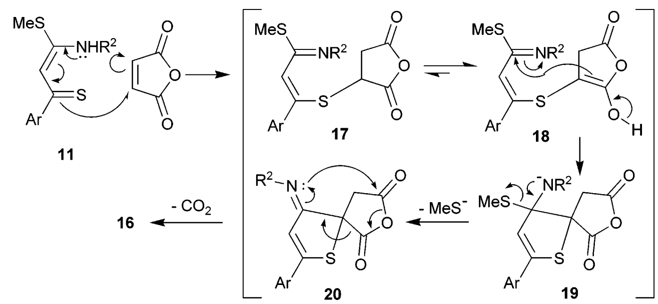
(86%), respectively. The result suggests the importance of an amide ion, which facilitates intramolecular nucleophilic displacement of an alkoxide to yield **14**. However, it is necessary to delineate the role of $BOC_2O$ and DMAP in view of the basicity of DMAP. In the meantime, the high yields of **14** resulting from the TMSOTf-derived reactions in the presence of $Et_3N$ may be rationalized on the basis of the intramolecular nucleophilic attack of the amino group of **8** onto the ester carbonyl carbon activated by the interaction of the carbonyl oxygen with TMSOTf. $Et_3N$ would be expected to trap the $CF_3SO_3H$ generated. Nucleophilic attack of cyanophenylamino groups of **8h** and **8k** onto $BOC_2O$ would give compounds **15h** and **15k**, respectively.

Heating compounds **14** in the presence of a catalytic amount of $Rh_2(OAc)_4{\cdot}2H_2O$ in PhH afforded 4-alkyl (and aryl)-2-aryl-5,6-dihydro-4*H*-thieno[3,2-*b*]pyrrol-5-ones **16**. Much better yields of **16** were obtained utilizing a catalytic amount of $Rh_2(CF_3CF_2CF_2CO_2)_4$ in place of $Rh_2(OAc)_4{\cdot}2H_2O$ (Scheme 6). Yields of **16** and reaction times are summarized in Table 2. Although compounds **16** are all new, an analogous type of ring contraction of diazoquinolines has been reported.[5,15]

Alternatively, compound **16a** was directly obtained from the reaction of **11a** with maleic anhydride **13** in various solvents such as PhH (2 h, 56%), $CH_3CN$ (45 min, 49%; 3 h, 52%), toluene (1.5 h, 34%), and $CH_2Cl_2$ (10 h, 92%) at reflux (Scheme 6). Similar treatment of **11b** in $CH_2Cl_2$ for 40 h gave **16b** in 41% yield. In addition, compounds **16n**−**p** were obtained in 76, 41, and 42% yields, respectively, using the corresponding starting materials **11n**−**p**. Yields were variable depending on the structures of **11**, and the reaction times were relatively longer compared with those in listed in Table 2.

The formation of **16** from **11** could be rationalized on the basis of Michael-type addition of the thione sulfur to maleic anhydride, leading to succinic anhydride derivative **17**, which equilibrates with its enol **18** (Scheme 7). Intramolecular nucleophilic attack of the enolic carbon of **18** to the imino carbon would give intermediate **19**. Loss of a methanethiolate ion from **19** gives 2,3-dihydrothiophene intermediate **20**, analogous to the intermediates proposed in the reactions of **11** with carbonyl compounds having active methylene hydrogen atoms in the presence of $Hg(OAc)_2$.[17] Intramolecular nucleophilic attack of the imino nitrogen to the carbonyl group of the succinic anhydride moiety, followed by decarboxylation, concomitant with aromatization of dihydrothiophene moiety, would result in the formation of **16**.

**SCHEME 7**




In summary, stirring 3-{3-alkyl (and aryl)amino-5-arylthieno-2-yl}-3-oxo-2-diazopropanoates with TMSOTf and $Et_3N$ in $CH_2Cl_2$ at room temperature produced diazothieno[3,2-*b*]pyridine-5,7-diones in excellent yields. The compounds underwent ring contraction reactions by heating in the presence of $Rh_2(CF_3CF_2CF_2CO_2)_4$ catalyst in PhH at reflux to give 5,6-dihydro-4*H*-thieno[3,2-*b*]-pyrrol-5-ones. Both classes of compounds are all newly discovered despite the existence of analogous compounds such as 2-diazocyclohexane-1,3-diones and diazoquinolinediones.

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**Supporting Information Available:** General procedure for the synthesis of **8**, **10**, **11**, and **14**−**16**, $^1H$ NMR, $^{13}C$ NMR, IR, and elemental analysis of **8a**−**m**, **11a**−**p**, **14a**−**m**, **15h**, **15k**, and **16a**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Kim, B. S.; Kim, K. *J. Org. Chem.* **2000**, *65*, 3690−3699.