Tetrahedron Letters 52 (2011) 3633–3635

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

3-Bromocyclohexane-1,2-dione as a useful reagent for Hantzsch synthesis of thiazoles and the synthesis of related heterocycles

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ARTICLE INFO

Article history:
Received 15 April 2011
Revised 29 April 2011
Accepted 5 May 2011
Available online 17 May 2011

Keywords:
3-Bromocyclohexan-1,2-dione
Hantzsch
Thiazole

ABSTRACT

We describe the use of 3-bromocyclohexane-1,2-dione, an air stable, versatile reagent for the Hantzsch thiazole synthesis and the synthesis of other closely related heterocycles.

Thiazoles are ubiquitous building blocks in medicinal chemistry and can be found in numerous natural products (e.g., epothilone) and biologically important compounds including the anticancer drug dasatinib, antiviral clinical candidate TMC435350, and antidiabetic drug candidate MB06322.[1–4] For a recent medicinal chemistry program, we looked to extend the utility of thiazoles to a bicyclic thiazole ring system. In this context, we required the intermediate 6,7-dihydrobenzo[*d*]thiazol-4(5*H*)-one **1** (Fig. 1). Compound **1** where R is methyl had previously been prepared via a multi-step synthesis from diethyl 2-oxoheptanedioate **2**.[5] As this method was not amenable to the rapid synthesis of various analogs, we designed a more expedient route to **1** using a Hantzsch reaction of 3-bromocyclohexane-1,2-dione **3** with appropriately substituted thioamides. This reaction has not been investigated in detail, although one example of Hantzsch thiazole synthesis using bromodiketone **3** and thioamides **4** was described by Denonne et al. in a patent application, but the yield was reported to be only 20%.[6] In contrast, 2-bromocyclohexane-1,3-dione **5** is widely known to undergo Hantzsch reaction with various thioureas and thioamides to give the regioisomeric 5,6-dihydrobenzo[*d*]thiazol-7(4*H*)-ones **6**.[7–9] We, therefore, undertook a series of studies intended to optimize the synthesis of bicyclic thiazoles **1**. This report describes the synthesis of pure bromodiketone **3** and its use in the preparation of bicyclic thiazoles and related heterocycles.

In our initial investigation, we prepared 3-bromocyclohexane-1,2-dione **3** from 1,2-cyclohexanedione using bromine (1 equiv) in carbon tetrachloride at 0 °C. The crude product after removal of the solvent was used immediately for the Hantzsch reactions under typical conditions (EtOH, reflux) as we were concerned about the stability of **3**. We did obtain the desired 6,7-dihydrobenzo[*d*]thiazol-4(5*H*)-ones **1**, but the yields were generally modest. We also explored the Hantzsch thiazole synthesis using bromodiketone **3** generated in situ following the procedure of Denonne et. al.[6] and again the yields were unsatisfactory. For example, only 21% yield of 2-(pyridin-4-yl)-6,7-dihydrobenzo[*d*]thiazol-4(5*H*)-one was obtained from pyridine-4-carbothioamide. During the optimization

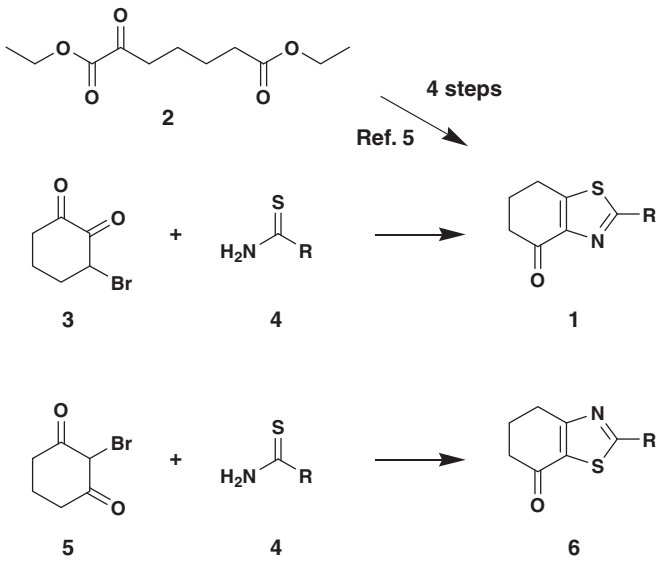

Figure 1. Hantzsch thiazole synthesis using bromodiketones.

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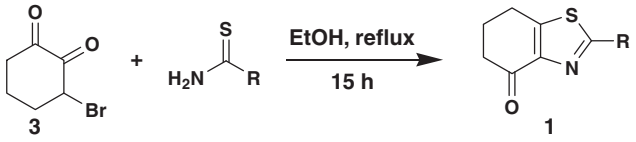
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.05.028

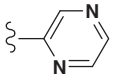
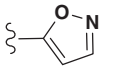
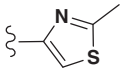
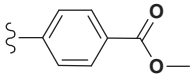
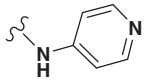
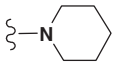
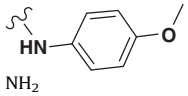
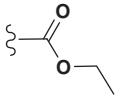
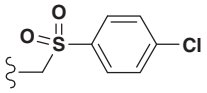
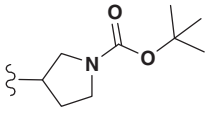
process, we observed by ^{1}H NMR analysis that the crude bromodiketone **3** was contaminated with several unidentified side products as well as a trace amount of hydrogen bromide and that it decomposed slowly even at −40 °C. This observation suggested that the yield could be improved if the decomposition was avoided. Preparation of pure **3** required considerable experimentation, and eventually we found that the crude material could be purified using a pad of Silica gel, eluting with 2.5% MeOH/$CHCl_3$ followed by trituration of the resulting white powder with minimal diethyl ether to give pure 3-bromocyclohexane-1,2-dione **3** as a white, crystalline solid as determined by ^{1}H NMR.[10] This purified material was found to be stable, with no special handling required. After one month in a clear vial at room temperature on the bench (no nitrogen flush), no degradation was detected by ^{1}H NMR analysis.

With pure bromodiketone **3** in hand, we examined its reaction with pyridine-4-carbothioamide in refluxing ethanol. Under conditions optimized for this substrate (1.5 equiv bromide **3**, 0.3 M in EtOH, reflux 15 h),[11] 2-(pyridin-4-yl)-6,7-dihydrobenzo[*d*]thiazol-4(5*H*)-one (Table 1, entry 1) was isolated in 76% yield, which is a significant improvement over that obtained using crude **3** following the patented procedure (vide supra; 21%). A similar yield was obtained from pyridine-2-carbothioamide (Table 1, entry 2), while

Table 1
Hantzsch reaction of **3** with thioamides and thioureas

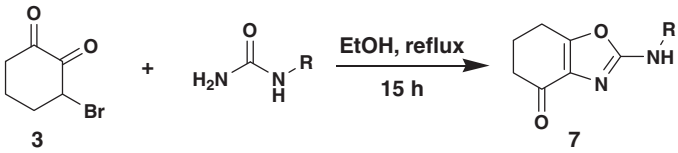


3 **1**

Entry	R	Yield[a,b] (%)
1	4-Pyridyl	76
2	2-Pyridyl	76
3	3-Pyridyl	54
4		76
5		68
6		80
7		50
8	Phenyl	73
9	2,4-Dichlorophenyl	72
10	Mesityl	67
11	4-Methoxyphenyl	53
12[c]		72
13	*tert*-Butyl	51
14	Ethyl	30
15	Cyclopropyl	29
16	Benzyl	33
17		83
18		64
19		49
20	NH_2	71
21		51
22		64
23		25[d]
24		Trace

[a] Isolated yield.
[b] Yields not optimized.
[c] Run in MeOH instead of EtOH due to transesterification.
[d] Small amount of BOC deprotected product also observed.

Table 2
Reaction of **3** with ureas

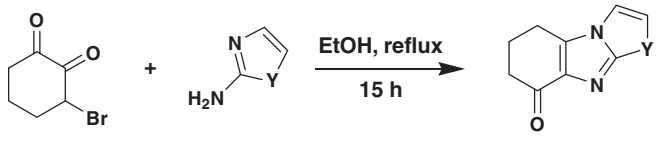


3 **7**

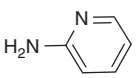
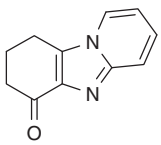
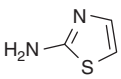
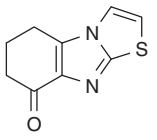
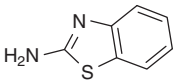
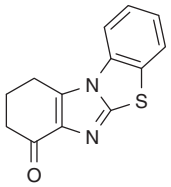
Entry	R	Yield[a,b] (%)
1	Methyl	41
2	Benzyl	72
3	Phenyl	60
4	2-Pyridyl	Trace
5	2-Chloroethyl	Trace

[a] Isolated yield.
[b] Yields not optimized.

Table 3
Tricyclic imidazole formation



3 **8**

Entry	Aminoheterocycle	Product	Yield[a,b] (%)
1			53
2			52
3			Trace

[a] Isolated yield.
[b] Yields not optimized.

pyridine-3-carbothioamide gave a somewhat lower yield (Table 1, entry 3). In addition to pyridine thioamides, reactions of **3** with pyrazine, isoxazole, thiazole, and imidazole thioamides also proceeded smoothly to afford heteroaryl substituted bicyclic thiazoles in good yields (Table 1, entries 4–7). When phenyl and substituted phenyl thioamides were used in these Hantzsch reactions, the yields were comparable to those from heteroaryl thioamides. Among several simple alkyl thioamides evaluated, *tert*-butylthioamide gave the highest yield (51%, Table 1, entry 13), and ethyl, cyclopropyl, and benzyl thioamides afforded modest yields (ca. 30%, Table 1, entries 14–16). Hantzsch-type cyclizations also proceeded efficiently for thiourea substrates, with the highest yield obtained from 1-(pyridin-4-yl)thiourea (Table 1, entry 17). A salient feature of this chemistry is that ester, sulfone, and *N*-BOC functional groups are well tolerated (Table 1, entries 12, 21–23). While the *N*-BOC pyrrolidine derivative (Table 1, entry 23) gave only a modest yield, this result is comparable to the other alkyl derivatives. However, only a trace amount of the desired product was observed in the reaction with 2-cyanoethanethioamide (Table 1, entry 24).

With the Hantzsch thiazole synthesis well established, we extended this methodology to the synthesis of bicyclic aminooxazoles. Exposure of bromodiketone **3** to methyl, benzyl, and phenyl ureas furnished the expected 2-aminooxazoles in good yields (Table 2, entries 1–3). In the cases of 2-pyridyl urea and 2-chloroethylurea, only a small amount of the desired 2-aminooxazole was formed.

Finally, we utilized bromodiketone **3** for the synthesis of some unique tricyclic imidazoles **8** (Table 3). Treatment of 3-bromocyclohexane-1,2-dione **3** with 2-aminopyridine and 2-aminothiazole in refluxing ethanol resulted in the formation of their respective tricyclic imidazole compounds in good yields (Table 3), although the 2-aminobenzothiazole gave only a trace amount of the desired product.

In summary, we have developed a convenient synthesis of pure, air-stable 3-bromocyclohexane-1,2-dione **3**. This bromide was shown to be a versatile reagent for the Hantzsch thiazole synthesis and the synthesis of other closely related heterocycles. The methodology described has been successfully applied to the synthesis of biologically active bicyclic thiazoles, and these compounds will be reported in due course. With the wide variety of commercially available thioamides, thioureas, amides, 2-aminothiazoles, and 2-aminopyridines, we anticipate widespread application of this procedure to the synthesis of various bicyclic thiazoles and oxazoles, as well as tricyclic imidazoles.

Acknowledgments

We would like to thank Dr. Lorin A. Thompson and Dr. John E. Macor for their encouragement.

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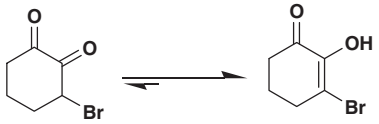
10. *Modified procedure for the preparation of 3-bromocyclohexane-1,2-dione* **3**. To a solution of 1,2-cyclohexanedione (5.1 g, 45.5 mmol) in diethyl ether (46 mL) at 0 °C was added Br_2 (2.34 mL, 7.27 g, 45.5 mmol) dropwise over 10 min. When the addition was complete, the reaction was allowed to come to room temperature and stir for 15 min., at which time the reaction mixture was concentrated in vacuo. The resulting dark oil was taken up in 2.5% MeOH/$CHCl_3$ and run through a pad of silica gel, eluting with the same solvent mixture. The solvent was then removed in vacuo and the resulting yellow solid was triturated with minimal cold diethyl ether (approx. 15 mL). Filtration gave 3-bromocyclohexane-1,2-dione as a white crystalline solid (4.1 g, 47%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (s, 1H), 2.90 (t, J = 6.0 Hz, 2H), 2.62–2.54 (m, 2H), 2.09 (dt, J = 13.0, 6.3 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.7, 146.0, 119.4, 35.5, 34.5, 22.9. The carbon data as well as an hmqc experiment which showed no cross peak of a carbon with the 6.43 ppm proton indicate that in solution, the dione **3** exists exclusively in the enol form.



11. *Typical procedure for coupling of 3-bromocyclohexane-1,2-dione* **3** *in Hantzsch and related reactions.* A mixture of 3-bromocyclohexane-1,2-dione **3** (50 mg, 0.26 mmol) and pyridine-4-carbothioamide (24.1 mg, 0.17 mmol) in EtOH (0.69 mL) was heated to reflux and stirred for 15 h. The reaction mixture was diluted with DMSO (0.5 mL) to completely dissolve all solids and the resulting mixture was purified by directly injecting the reaction mixture into a preparatory HPLC (C_{18}, water/acetonitrile/ammonium acetate buffer) to give 2-(pyridin-4-yl)-6,7-dihydrobenzo[*d*]thiazol-4(5*H*)-one (30.4 mg, 0.13 mmol, 76%) (Table 1, entry 1). LC-MS $(M+H)^+$ = 231.1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80–8.69 (m, 2H), 7.95–7.80 (m, 2H), 3.22 (t, J = 6.1 Hz, 2H), 2.76 (dd, J = 7.2, 6.0 Hz, 2H), 2.38–2.29 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 190.9, 163.3, 152.7, 150.9, 150.5, 139.7, 120.8, 38.3, 24.6, 23.9.