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N-Chlorophthalimide as a mild and efficient chlorination reagent in the Gassman *ortho* alkylation of aromatic amines. Synthesis of 3-(methylthio)oxindoles

Marcin Cybulski [a,*], Adam Formela [a], Izabela Fokt [b]

[a] *Pharmaceutical Research Institute, 8 Rydygiera Street, 01-793 Warsaw, Poland*
[b] *The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA*

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ABSTRACT

A practical modification of the Gassman 3-(methylthio)oxindole synthesis is reported. In our method, substituted anilines and 2-(methylthio)acetamide were reacted under mild reaction conditions, in the presence of *N*-chlorophthalimide as a chlorinating agent to give α-amidosulfides, which, in the next step of the process, were cyclized to give 3-(methylthio)oxindoles. The method was successfully applied for the synthesis of the key intermediate, 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide, in the process of the preparation of nepafenac, a commonly used ophthalmic drug.

The indole system is one of the most common heterocycles in nature.[1] The indole moiety is present in biologically active alkaloids such as the plant-derived, so called vinca alkaloids, vinblastine, and vincristine, as well as in many synthetic medicinal compounds.[2–4] The synthesis of differently substituted indole rings has long-inspired organic chemists.[5–8]

The choice of the method used depends on the type and availability of the starting material, type of substituents in such substrates, safety, and practicality, especially when a multigram amount of product needs to be prepared.

Numerous methods for the synthesis of indoles have been developed, among them the Gassman synthesis. In the Gassman method, *N*-chloroanilines react with β-keto sulfides or α-carboalkoxy sulfides to yield azasulfonium salts, which when treated with a base led to 3-methylthioindoles or 3-(methylthio)oxindoles, respectively (Scheme 1).

Subsequent reduction of 3-methylthioindoles or 3-methylthiooxindoles obtained using Raney-Nickel as the catalyst led to the appropriate indoles or oxindoles.[9–12]

A major limitation of this method is the stability of *N*-chloroanilines formed during the first step of the process, which strongly depends on the type and position of the substituents on the aromatic ring. In all reported conditions applied for the Gassman reaction, temperatures of −65 °C or lower, as well as anhydrous solvents and an inert atmosphere are required.[13–16] Chlorinating agents reported in the literature such as *tert*-butyl hypochlorite or chlorine[15] are difficult to handle, especially when a multigram amount of the substituted indole needs to be synthesized. The Gassman method is a one-pot chemical process, and because of their low stability, none of the intermediates are isolated.

We previously developed a new method for the synthesis of nepafenac, a non-steroidal anti-inflammatory drug, commonly used to treat eye pain, redness, and swelling in patients recovering from cataract surgery.[17] The key step of the process was the development of an efficient method for the synthesis of an α-amidosulfide intermediate. While using classical conditions for Gassman *ortho* alkylation of aromatic amines, we obtained a mixture of 2-amino-5-chlorobenzophenone and 2-(2-amino-3-benzoyl-5-chlorophenyl)-2-(methylthio)acetamide along with the required 2-(2-amino-3-benzoylphenyl)-2-(methylthio)acetamide.[17] While searching for a milder, more stable, and easy to handle (on a large scale) source of chlorine for the Gassman *ortho*-alkylation of aniline, we found that *N*-chlorophthalimide was suitable. In this Letter, we present our studies on the limitations and usefulness of *N*-chlorophthalimide for the synthesis of α-amidosulfides. The α-amidosulfides obtained can be used for the synthesis of 3-(methylthio)oxindole via very efficient cyclization under mild acidic conditions (Table 1), and also as building blocks in other processes. Table 1 also includes the previously published yield of product **4a**, and the overall yields of **5a–f** were obtained using the original Gassman one-pot method. The stability of *N*-chlorophthalimide and its mild reactivity allowed us to carry out all the processes in ACS-grade solvents (no need for additional

* Corresponding author. Tel.: +48 22 456 39 40; fax: +48 22 456 39 00.
E-mail address: m.cybulski@ifarm.eu (M. Cybulski).

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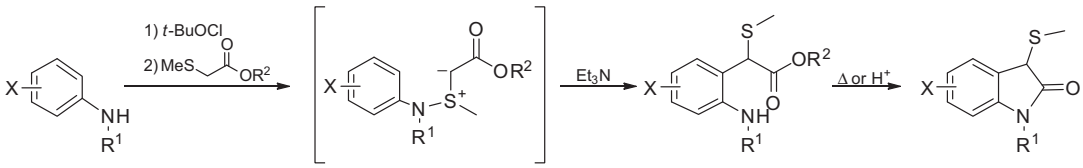


Scheme 1. Mechanism of the Gassman synthesis of oxindoles from substituted anilines.[15,20]

Table 1
3-(Methylthio)oxindole synthesis in the presence of *N*-chlorophthalimide

Step I				Step II			Overall yield (%)	Overall yield Reference data (%)
Substrate	Product	Yield (%)	Reference data (%)	Substrate	Product	Yield (%)		
1a	**4a**	59	84[15]	**4a**	**5a**	97	57	78[15]
1b	**4b**	41	—	**4b**	**5b**	98	40	34[16]
1c	**4c**	55	—	**4c**	**5c**	92	51	77[19]
1d	**4d**	22	—	**4d**	**5d**	85	19	12[12]
1e	**4e**	13	—	**4e**	**5e**	75	10	Traces[15]
1e	**4f**	17 (mixture with **5f**)	—	**4f**	**5f**	95	16	61[16]

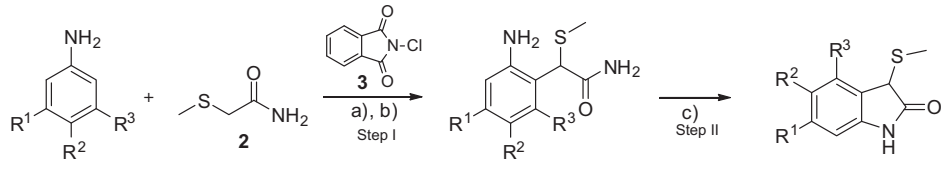
drying) without an inert atmosphere. All the reactions were performed over a temperature range of −20 °C to −8 °C, which is higher than when *tert*-butyl hypochlorite or chlorine was used (−65 °C and lower). To study the usefulness of *N*-chlorophthalimide in such a process, several novel (**4b**–**f**) as well as known amide (**4a**) and their cyclized analogs (**5a**–**f**) were prepared under the conditions previously described[17] (Scheme 2). Starting from *para*-substituted methyl (**1b**), chloro (**1c**), and nitro (**1d**) we obtained the corresponding substituted 2-(methylthio)acetamides. No such compounds were reported in the literature. For a *meta*-nitro-substituted aniline (**1e**), Gassman reported the formation of **5f** as the only product.[12] Using our method, we were able to obtain both regioisomers **5e** and **5f**. This is as a result of the intramolecular attack of the generated ylide on either the *ortho* or *para* positions of aniline. For the first time, we were able to obtain oxindole **5e** with a nitro substituent at position 6. Similar to the original Gassman conditions (2% yield in the original Gassman paper[12]), in our method, we were not successful when anisidine with a strong electron-donating *para*-methoxy group was used as the substrate.

In conclusion our results show that the present modification offers an attractive alternative to other chlorinating agents available for the preparation of oxindoles via the Gassman procedure. In the reports of Gassman,[10–12,16] substituted phenyl-2-(methylthio)acetates, which were obtained in the first step of the process, were not isolated because of their instability and were therefore immediately cyclized into oxindoles. In our method, by using 2-methylacetamide as the starting material in the first step of the process, we obtained stable substituted phenyl-2-(methylthio)acetamides, which allowed them to be isolated and fully characterized. Under acidic conditions such compounds easily cyclize into the corresponding oxindoles in high yields. Although the overall yield of our two-step process is comparable to that reported by Gassman for the direct process of oxindole preparation, the ease of manipulation (higher temperature, non-anhydrous solvents, and an easy-to-handle chlorinating agent) of our route might be attractive to chemists. We did not optimize the conditions of the process, therefore, it is our belief that further optimization may improve the yields further. The use of *N*-chlorophthalimide allowed us, for the first time using the Gassman procedure, to obtain an oxindole derivative with a nitro group at position 6 of the indole ring.

General experimental procedures (GP)

ortho alkylation (GP1)

A vigorously stirred suspension of aniline **1a**–**e** (8.9 mmol) and 2-(methylthio)acetamide (**2**)[18] (0.94 g, 8.9 mmol) in CH_2Cl_2 (40 mL) was cooled to −20 °C. A solution of *N*-chlorophthalimide (**3**) (1.62 g, 8.9 mmol) in CH_2Cl_2 (55 mL) was added dropwise, while the temperature was maintained between −20 °C and −15 °C. The obtained mixture was stirred at −20 °C to −15 °C for 2 h, and then was allowed to warm to ~−8 °C. Et_3N (1.35 mL, 9.7 mmol) was added and the mixture was washed with 1 M KOH aqueous solution (3 × 20 mL) and then with H_2O until neutral, and dried over anhydrous $MgSO_4$. The solvents were removed and the residue was purified by column chromatography over silica gel with EtOAc–hexanes (gradient) as eluent.



1a $R^1 = R^2 = R^3 = H$
1b $R^1 = R^3 = H$, $R^2 = CH_3$
1c $R^1 = R^3 = H$, $R^2 = Cl$
1d $R^1 = R^3 = H$, $R^2 = NO_2$
1e $R^1 = NO_2$, $R^2 = R^3 = H$

4a $R^1 = R^2 = R^3 = H$
4b $R^1 = R^3 = H$, $R^2 = CH_3$
4c $R^1 = R^3 = H$, $R^2 = Cl$
4d $R^1 = R^3 = H$, $R^2 = NO_2$
4e $R^1 = NO_2$, $R^2 = R^3 = H$
4f $R^1 = R^2 = H$, $R^3 = NO_2$

5a $R^1 = R^2 = R^3 = H$
5b $R^1 = R^3 = H$, $R^2 = CH_3$
5c $R^1 = R^3 = H$, $R^2 = Cl$
5d $R^1 = R^3 = H$, $R^2 = NO_2$
5e $R^1 = NO_2$, $R^2 = R^3 = H$
5f $R^1 = R^2 = H$, $R^3 = NO_2$

Scheme 2. Synthesis of various substituted 3-(methylthio)oxindoles. Step I: (a) *N*-chlorophthalimide (**3**), CH_2Cl_2, (b) Et_3N, KOH (aq); Step II: (c) HCl (aq).

2-(2-Aminophenyl)-2-(methylthio)acetamide (4a)

Yield 59%, mp 95–96 °C.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.54 (br s, 1H, NH), 7.22 (br s, 1H, NH), 7.20 (dd, 1H, J = 7.7 Hz, J = 1.5 Hz), 6.90 (m, 1H), 6.64 (dd, 1H, J = 7.9 Hz, J = 1.1 Hz), 6.52 (ddd, 1H, J = 7.9 Hz, J = 7.7 Hz, J = 1.5 Hz), 5.18 (br s, 2H, NH_2), 4.56 (s, 1H, CHS), 1.96 (s, 3H, SMe).

^{13}C NMR (600 MHz, DMSO-d_6): δ = 171.5, 146.9, 129.3, 128.1, 119.8, 116.1, 115.5, 50.9, 14.5.

HRMS (ESI): calcd for $C_9H_{12}N_2OSNa$ [M+Na]$^+$: 219.0568; found: 219.0565.

3-(Methylthio)oxindole formation (GP2)

A suspension of α-amidosulfide **4a–f** in 2 M HCl (10 mL/4 mmol) was prepared and stirred at room temperature while the progress of the reaction was monitored by TLC. After the reaction was complete, the obtained solid product was filtered, washed with H_2O until neutral and air dried.

3-(Methylthio)indolin-2-one (5a)

Yield 97%, mp 132–133 °C, Lit.[12] 126–127 °C

^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.50 (br s, 1H, NH), 7.16–7.28 (m, 2H), 6.98 (dd, 1H, J = 7.7 Hz, J = 7.7 Hz), 6.82 (d, 1H, J = 7.7 Hz), 4.49 (s, 1H, CHS), 1.96 (s, 3H, SMe).

^{13}C NMR (600 MHz, DMSO-d_6): δ = 176.1, 142.5, 128.7, 126.6, 124.8, 121.8, 109.4, 45.3, 11.8.

HRMS (ESI): calcd for C_9H_9NOSNa [M+Na]$^+$: 202.0303; found: 202.0294.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.08.044.

References and notes

1. Van Order, R. B.; Lindwall, H. G. *Chem. Rev.* **1942**, *30*, 69.
2. Wu, Y. J. In *Heterocyclic Scaffolds II: Reaction and Applications of Indoles*; Gribble, G. W., Ed.; Springer-Verlag: Berlin Heidelberg, 2010; pp 1–30.
3. de Sa Alves, F. R.; Barreiro, E. J.; Manssour, F.; Carlos, A. *Mini-Rev. Med. Chem.* **2009**, *9*, 782.
4. Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Kumar, A.; Choi, E. H. *Molecules* **2013**, *18*, 6620.
5. Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875.
6. Taber, D. F.; Tirunahari, P. K. *Tetrahedron* **2011**, *67*, 7195.
7. Miller, M.; Tsang, W.; Merritt, A.; Procter, D. J. *Chem. Commun.* **2007**, 498.
8. Miller, M.; Vogel, C. J.; Tsang, W.; Merrit, A.; Procter, D. J. *Org. Biomol. Chem.* **2009**, *7*, 589.
9. Gassman, P. G.; Gruetzmacher, G. *J. Am. Chem. Soc.* **1973**, *95*, 588.
10. Gassman, P. G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 591.
11. Gassman, P. G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 590.
12. Gassman, P. G.; Gruetzmacher, G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5512.
13. Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett.* **1983**, *24*, 2437.
14. Wright, S. W.; McClure, L. D.; Hageman, D. L. *Tetrahedron Lett.* **1996**, *37*, 4631.
15. Gassman, P. G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*, 5508.
16. Gassman, P. G.; Van Bergen, T. J. *J. Am. Chem. Soc.* **1973**, *95*, 2718.
17. Cybulski, M.; Formela, A.; Mucha, M.; Klos, K.; Roszczynski, J.; Winiarski, J. *Lett. Org. Chem.* **2012**, *9*, 461.
18. Mori, Y.; Fujiwara, S.; Miyachi, T.; Kitanishi, H.; Oya, M.; Yamamoto, K.; Suzuki, M. *Chem. Pharm. Bull.* **1983**, *31*, 1505.
19. Gassman, P. G.; Gilbert, D. P.; Luh, T. Y. *J. Org. Chem.* **1977**, *42*, 1340.
20. Li, J. J. In *Name Reactions*, 4th ed.; Li, J. J., Ed.; Springer-Verlag: Berlin Heidelberg, 2009; pp 251–252.