Iodine-Mediated Guanidine Formation through Arylsulfonyl-Activated Thioureas

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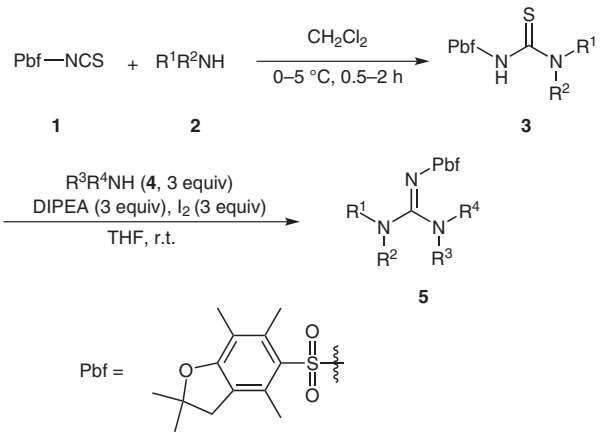
Abstract: Reaction of arylsulfonyl thioureas with amines to form guanidines can be efficiently promoted through the use of iodine, instead of conventional reagents such as the Mukaiyama reagent or EDC. The general scope and limitations of the reaction are probed.

Key words: iodine, guanidine, arylsulfonyl thiourea, desulfurizations, aminations

Guanidine functional groups play essential roles in biological systems, natural products and synthetic pharmaceuticals.[1] Consequently, many reagents have been developed to prepare protected or unprotected guanidines.[2] One of the common strategies used for the construction of the guanidine functionality is transformation from thioureas. Such reactions are usually promoted through reaction with EDC,[3] Hg(II),[4] the Mukaiyama reagent (2-chloro-1-methylpyridinium iodide),[5] or 2,4-dinitrofluorobenzene.[3] In all these cases the thiourea needs to be substituted by electron-withdrawing groups such as aryl, acyl, or alkoxycarbonyl groups in order to achieve high yields.[6] We have previously reported the synthesis of N′,N″-disubstituted or oligomeric guanidines through the use of Mukaiyama reagent or EDC-mediated condensation with Pbf-activated thiourea (Pbf: 2,2,4,6,7-pentamethyl-dihydrobenzofuran-5-sulfonyl).[7] Furthermore, this approach provides efficient access to heterocycles such as 1,5-disubstituted 2-(*N*-alkylamino)imidazolidin-4-ones[8] and 2-(*N*-alkylamino)pyrimidin-4-one derivatives.[9] The method of using Pbf-activated thiourea was also applied to the preparation of N^G-substituted L-arginine analogues that are suitable for solid-phase peptide synthesis.[10] Similarly, other acid-sensitive arylsulfonyl activation groups such as Pmc could be incorporated into the guanidine synthesis (Pmc: 2,2,5,7,8-pentamethylchroman-6-sulfonyl).[11] The strong activating ability of the Pbf group prompted us to investigate whether a milder and less toxic reagent could be used for the guanidine formation reaction, which is believed to proceed through desulfurization and a carbodiimide intermediate. The ability of iodine to act as a desulfurization reagent in the cyclization of *N*-2-pyridylmethyl thioamides or benzothiazoles attracted our attention because iodine is an easy to handle, low cost, and low toxicity reagent.[12] Herein, we wish to report our investigation of iodine as a desulfurization reagent to promote guanidine formation using Pbf-activated thioureas.

Pbf-activated thioureas **3** were conveniently prepared in high yield (Scheme 1) in dichloromethane according to reported procedures[7c,9] from alkyl or aryl amines, including secondary amines, with the highly reactive Pbf-isothiocyanate. Pbf-isothiocyanate may be easily obtained by treatment of Pbf-Cl with Bu_4NNCS directly[7c] or from Pbf-NH_2 treated with KOH and CS_2 followed by triphosgene in toluene, similar to the preparation of Pmc-isothiocyanate.[11]

The thioureas **3** thus obtained were treated with a diverse array of amines **4** (R^3R^4NH) to produce *N*-Pbf-*N*′,*N*″-disubstituted guanidines in the presence of iodine (Table 1). A general procedure is described here. At room temperature, solid iodine (3 equiv) was added slowly to a stirring mixture of thiourea **3** (1 equiv) and DIPEA (3 equiv) in an aprotic solvent such as THF. Iodine dissolved immediately and the reaction mixture became a purple clear solution. This was followed by addition of **4**. While most guanidine products were formed within two hours (monitored by TLC), the reactions were still maintained overnight in order to allow slower reactions to proceed more completely for yield comparison. In our experience, heating or changing solvent to DMF or CH_2Cl_2 did not significantly change the product yield. The desired guanidines **5** were afforded as white solids after silica gel chromatography using ethyl acetate and petroleum ether as eluent.[13]



Scheme 1

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The results of the iodine-mediated guanidine formation is shown in Table 1. There are several findings in our results that are worth noting. First, in general, the iodine-promoted reaction of Pbf-thioureas with both primary and secondary amines produced the desired guanidines in good yields (Table 1, entries 1, 2, 4, 6, 9, 11, and 13–15). Second, reactions with ethanolamine or β-amine acid esters gave lower, but still reasonable, yields (Table 1, entries 7, and 16–18). This result showed that the reaction can easily tolerate a range of substituted functional groups such as hydroxy or ester groups on the amine or the thiourea moieties. Third, aromatic amines with a strong electron-withdrawing substituent, such as a nitro group, failed to undergo the guanidine formation reaction (Table 1, entries 5 and 12). The result suggested that aromatic amines must possess sufficient nucleophilicity to form the guanidine (Table 1, entries 3, 8, 10, and 15). Fourth, N′,N′-disubstituted *N*-Pbf-thioureas (R^1 and $R^2 \neq H$) failed to afford guanidines under our reaction conditions, suggesting that thioureas incompatible with the pathway of generating a carbodiimide intermediate would not work (Table 1, entries 20 and 21). This result was consistent with guanidinylation reactions of other activated thioureas in general using EDC or the Mukaiyama reagent, including guanidinylation by Pmc-thiourea with EDC.[11]

The desulfurization ability of iodine in the guanidinylation process of Pbf-activated thioureas was compared to those of the Mukaiyama reagent and EDC. As shown in Table 1 (entries 1, 4, 5, 7, 12, and 17–19), in general, iodine produced similar yields to those obtained from reactions promoted by either EDC or the Mukaiyama reagent.

Table 1 Conversion of Pbf-thiourea and Amines into Guanidines

Entry	R^1R^2NH (**2**)	Thiourea (**3**)	R^3R^4NH (**4**)	Product (**5**)	Yield with iodine (%)[a]	Yield with EDC (%)[a]	Yield with Mukaiyama reagent (%)[a]
1	*n*-$BuNH_2$	**3a**	piperidine	**5a**	94[b]	99	96
2	*n*-$BuNH_2$	**3a**	$BnNH_2$	**5b**	83	–[c]	–
3	*n*-$BuNH_2$	**3a**	4-$MeOC_6H_4NH_2$	**5c**	67	–	–
4	*n*-$BuNH_2$	**3a**	*n*-$BuNH_2$	**5d**	57	55	73
5	*n*-$BuNH_2$	**3a**	2-$ClC_6H_4NH_2$		0	0	0
6	*i*-$BuNH_2$	**3b**	Et_2NH	**5e**	89	–	–
7	*i*-$BuNH_2$	**3b**	$HO(CH_2)_2NH_2$	**5f**	88	84	74
8	*i*-$BuNH_2$	**3b**	4-$MeOC_6H_4NH_2$	**5g**	73	–	–
9	$PhNH_2$	**3c**	$BnNH_2$	**5h**	78	–	–
10	$PhNH_2$	**3c**	4-$MeOC_6H_4NH_2$	**5i**	77	–	–
11	$PhNH_2$	**3c**	morpholine	**5j**	71[b]	–	–
12	$PhNH_2$	**3c**	4-$O_2NC_6H_4NH_2$		0	0	0
13	$BnNH_2$	**3d**	pyrrolidine	**5k**	90	–	–
14	$BnNH_2$	**3d**	$BnNH_2$	**5l**	86	–	–
15	$BnNH_2$	**3d**	$PhNH_2$	**5h**	70	–	–
16	$BnNH_2$	**3d**	$Bn[MeCO_2(CH_2)_2]NH$ (HCl salt)	**5m**	67	–	–
17	$BnNH_2$	**3d**	$HO(CH_2)_2NH_2$	**5n**	60	56	50
18	$BnNH_2$	**3d**	$EtO_2C(CH_2)_2NH_2$ (HCl salt)	**5o**	54	70	85
19	$EtO_2C(CH_2)_2NH_2$ (HCl salt)	**3e**	$BnNH_2$	**5o**	63	79	90
20	piperidine	**3f**	$BnNH_2$		0[b]	–	–
21	Ph(Me)NH	**3g**	*n*-$BuNH_2$		0[b]	–	–

[a] Isolated yield.
[b] Solvent: CH_2Cl_2.
[c] Not performed.

In the case of reactions involving substrates with an ester group, iodine-promoted reactions gave slightly lower, but still reasonable, yields (entries 18 and 19 gave 54–63% for iodine *vs* 70–90% for EDC or the Mukaiyama reagent). Thus, we can conclude that, in general, iodine can replace EDC or the Mukaiyama reagent as an alternative low cost and low toxicity reagent in guanidinylation reactions with Pbf-activated thiourea.

Other thiourea guanidinylation reagents such as *N*,*N*′-bis(Boc)thiourea and *N*-phenyl-*N*′-benzyl thiourea[14] were also studied under our reaction conditions. However, guanidine products were not formed. The result shows that Pbf activates thiourea sufficiently enough to allow the use of iodine as a mild desulfurization reagent. We also believe that other arylsulfonyl-activated thioureas, for example Pmc-thiourea,[15] could achieve similar results using iodine in place of EDC or the Mukaiyama reagent.

In summary, iodine was found for the first time to be useful for the construction of guanidines from readily accessible Pbf-activated thioureas under mild conditions. Thus, iodine can be used as an economical and less toxic alternative to traditional reagents such as EDC or the Mukaiyama reagent. Application of this method for the synthesis of biologically active guanidine-containing heterocycles is currently under way in our group.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(13) **[*N*-(2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl)-*N*′-(2-ethoxycarbonylethyl)-*N*″-benzyl guanidine (5o):** Iodine (0.0928 g, 0.35 mmol) was added to a solution of thiourea **3e** (0.0495 g, 0.12 mmol) dissolved in THF (4 mL), followed by DIPEA (0.0491 g, 0.35 mmol). After 10 min, $BnNH_2$ (0.0388 g, 0.35 mmol) was added to the mixture, and the reaction mixture was stirred overnight at room temperature. The residue obtained after evaporation of the solvent was separated by silica gel column (petroleum ether–EtOAc) to afford **5o** as a white solid (0.0364 g, 63%). MS: *m*/*z* = 502.3 $[M + H]^+$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20–1.25 (t, *J* = 7.2 Hz, 3 H), 1.47 (s, 6 H), 2.10 (s, 3 H), 2.46–2.48 (d, *J* = 5.7 Hz, 2 H), 2.50 (s, 3 H), 2.58 (s, 3 H), 2.95 (s, 2 H), 3.44–3.50 (m, 2 H), 4.03–4.10 (m, 2 H), 4.30–4.32 (m, 2 H), 7.18–7.20 (m, 2 H), 7.29–7.31 (m, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.4, 14.1, 17.9, 19.2, 21.0, 28.6, 33.9, 36.9, 43.2, 45.4, 60.9, 86.3, 117.3, 124.4, 127.1, 127.8, 127.8, 132.3, 133.2, 138.4, 154.7, 158.6, 172.7. Anal. Calcd for $C_{26}H_{35}N_3O_5S$: C, 62.25; H, 7.03; N, 8.38. Found: C, 62.14; H, 7.12; N, 8.57.

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