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Tandem synthesis of [1,2,4]-triazoles mediated by iodine—a regioselective approach

Srimanta Guin, Saroj Kumar Rout, Nilufa Khatun, Tuhin Ghosh, Bhisma K. Patel *

Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati 781 039, India

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ABSTRACT

A tandem regioselective one-pot synthesis of 3-amino-[1,2,4]-triazoles has been achieved from 1,3-disubstituted thioureas using molecular iodine. In this one-pot strategy, the intermediate carbodiimide generated in situ from thiourea upon reaction with $HCONHNH_2$ gives diaryl/alkylhydrazinecarboximidamide or acylureidrazone, which then undergoes an intramolecular cyclodehydration to afford the corresponding 3-amino-[1,2,4]-triazole. The product regioselectivity for unsymmetrical 1,3-disubstituted thioureas correlate well with the pK_as of the parent amines attached, in which the amine having higher pK_a goes to the ring nitrogen while the other nitrogen remains flanked as an exocyclic nitrogen of the triazole core. This method is milder and environmentally sustainable giving good to excellent yields of the desired products.

1. Introduction

Chemistry to have its maximal effect on biology, discovery, and development of efficient synthetic methods for the construction of *N*, *O*, *S* heterocycles are in great demand in the field of chemical genetics.[1] As a privileged fragment, [1,2,4]-triazole core holds a central position in modern heterocyclic chemistry principally due to its prevalence in a wide variety of biologically active/relevant molecules, which are reported to exhibit diverse biological activities in the field of medicinal and agrochemicals.[2–5] Some examples of pharmaceutically significant compounds containing [1,2,4]-triazole nucleus are shown in Fig. 1.

The widespread applications of such potent 3-amino-[1,2,4]-triazoles have resulted in the development of numerous protocols for their synthesis. The general protocols for solution phase synthesis of 3-amino-[1,2,4]-triazoles involve the reaction of amidrazones with carbodiimides,[6a,b] cyclization of hydrazones,[6c] reaction of aminoguanidines with carboxylic acids.[6d] These processes entail direct condensation of thioamides with hydrazides, but are disadvantageous with respect to their commercial availability and diversities. Solid-phase synthesis has emerged as an important method for the construction of a library of organic compounds in combinatorial science and hence several methods are being developed in order to culminate the problems associated with solution phase methods.[7a–c] Stocks and co-workers have demonstrated a one-pot three component synthesis of [1,2,4]-triazole using acetic hydrazide, primary amine and DMFDMA (1,1-dimethoxy-*N*,*N*-dimethylmethamine) in which the desired triazole core is formed finally by a cyclodehydrative path.[8] An addition–dehydration path for the synthesis of 3-amino-[1,2,4]-triazoles has been documented by Chorev et al. in which a one-pot reaction of 1,3-disubstituted thiourea and acyl hydrazide was performed in the presence of toxic $Hg(OAc)_2$ as the thiophilic reagent.[9] Kamenecka group have reported a multi-stepped synthesis of 3-amino-[1,2,4]-triazoles through an oxidative approach. The thiourea or semithiocarbazide is initially oxidized to their corresponding sulfonic acid, which when reacted with amine or hydrazine followed by the treatment of trimethyl orthoformate

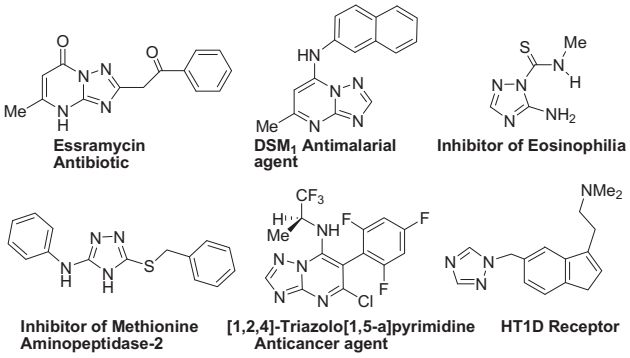

Fig. 1. Some pharmaceutical products having [1,2,4]-triazole core.

* Corresponding author. E-mail address: patel@iitg.ernet.in (B.K. Patel).

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afforded the corresponding triazole through a condensation–dehydration process.[10] Recently, Castanedo et al. have reported an intriguing synthesis of 1,3,5-substituted [1,2,4]-triazoles using carboxylic acids, amidines and hydrazines as the precursors.[11] Further, Wong et al. have described two elegant methods, one for the synthesis of 3,5-disubstituted [1,2,4]-triazole from aldehydes with hydrazonoyl hydrochloride via a 1,3-dipolar cycloaddition reaction[12a] and the other for the synthesis of 1,3,5-trisubstituted [1,2,4]-triazole by reacting oxime with hydrazonoyl hydrochloride.[12b]

Despite the numerous procedures enumerated in literature for the synthesis of [1,2,4]-triazoles possessing varied substitutions, few of these describe direct synthesis of the triazole having no substitution at the 5-position. Additionally, most of them suffer from severe environmental concerns as they involve direct or indirect use of strong alkaline or acidic conditions; toxic, corrosive and expensive reagents, which at times impede the applicability of these methodologies. Further, the generality of these methods are bound owing to (a) limited substrate scope, (b) not being atom-economical and (c) low yielding. Hence it is of utmost importance to develop a more sustainable synthesis of [1,2,4]-triazoles.

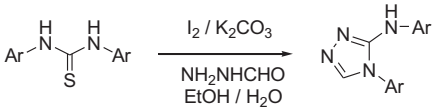
In recent years, molecular iodine has been identified as an efficient catalyst for various organic transformations pertaining to its low cost, non-toxicity, easy availability and eco-friendly nature.[13] Also as a part of our ongoing research program intended towards greener synthesis we have developed several synthetically useful transformations exploiting the desulfurative ability of molecular iodine.[14] So, from the 'Green Chemistry' perspective and our incessant effort to explore the utility of molecular iodine as an efficient thiophilic agent, herein, we envisaged a one-pot tandem strategy for the synthesis of 3-amino-[1,2,4]-triazoles from 1,3-disubstituted thioureas using molecular iodine as the desulfurizing agent. For [1,2,4]-triazoles derived from unsymmetrical thioureas it would be interesting to find out the product regioselectivity as which of the nitrogen would be part of the ring nitrogen in the triazole core and, which one to remain as an exocyclic nitrogen.

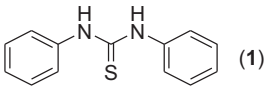
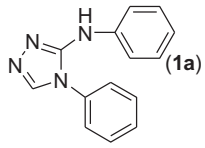
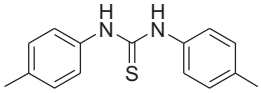
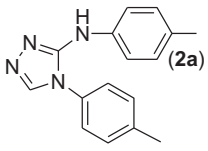
The genesis of the work started with two of our recent works on a green synthetic protocol for the preparation of carbodiimides[14d] from 1,3-disubstituted thioureas in the presence of molecular iodine and the synthesis of aminotetrazoles through the intermediacy of carbodiimide.[14e] Taking cues from these observations, we thought of developing an environmentally benign one-pot strategy for the synthesis of 3-amino-[1,2,4]-triazoles. In this methodology, the in situ generated carbodiimide from 1,3-disubstituted thiourea on treatment with formic hydrazide ($HCONHNH_2$) would form acylureidrazone, which is expected to undergo dehydrative cyclization to afford the targeted 3-amino-[1,2,4]-triazole.

2. Results and discussion

To test the feasibility of our envisioned route, in a typical reaction, to a solution of 1,3-diphenylthiourea (1 equiv) **1** in ethanol were added sequentially $HCONHNH_2$ (1 equiv), aqueous solution of K_2CO_3 (2.5 equiv) and iodine (1.1 equiv) pinch wise over a period of 10 min at room temperature. Formation of a new product along with other minor side products was observed together with the retention of some starting substrate **1**. Isolation by usual workup procedure followed by chromatographic purification (55% isolated yield) and characterization revealed the product to be phenyl-(4-phenyl-4*H*-[1,2,4]triazol-3-yl)-amine **1a**. Further optimization such as increasing the quantity of $HCONHNH_2$ to 2.5 equiv and iodine to 2 equiv, improved the isolated yield up to 81% with complete disappearance of **1**. Other inorganic carbonates such as Na_2CO_3 and Cs_2CO_3 were also found to be equally effective. Since we wanted to develop a greener protocol the organic bases or other environmentally non-compatible solvents were not studied for this transformation. The mechanistic path for this transformation is expected to be similar to the one already proposed by Chorev et al.[9] The intermediacy of carbodiimide has been confirmed by performing the reaction with an isolated carbodiimide.[14d] However, in none of the reaction, formation of the intermediate carbodiimide could be detected, probably due to the faster nucleophilic attack of $HCONHNH_2$ to intermediate carbodiimide than its formation in a polar protic medium. Interestingly, despite the presence of water in the medium, no urea by product was observed from the expected carbodiimide intermediate probably owing to the more nucleophilic nature of the formic acid hydrazide (NH_2NHCHO) compared to water. Employing this one-pot strategy, we have successfully prepared a series of [1,2,4]-triazol-3-yl-amines from their corresponding thioureas as shown in Table 1. Symmetrical thioureas **1**–**7** afforded their corresponding [1,2,4]-trizol-3-yl-amines **1a**–**7a** in good to excellent yields (Table 1). Symmetrical thioureas **2**–**5**

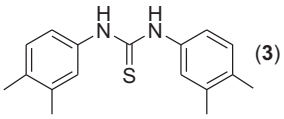
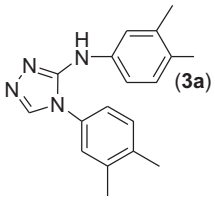
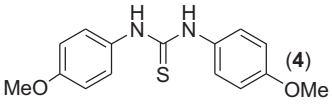
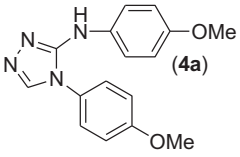
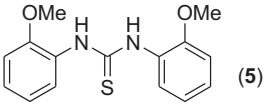
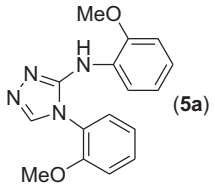
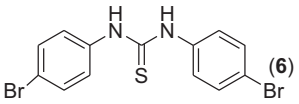
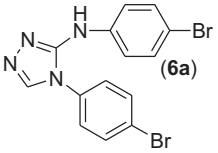
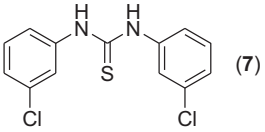
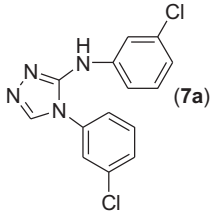
Table 1
Formation of [1,2,4]-triazol-3-yl-amine from symmetrical thiourea[a]



Substrate	Product[b]	Yield[c] (%)
 (**1**)	 (**1a**)	81
 (**2**)	 (**2a**)	83

(*continued on next page*)

Table 1 (*continued*)

Substrate	Product[b]	Yield[c] (%)
 (**3**)	 (**3a**)	75
 (**4**)	 (**4a**)	80
 (**5**)	 (**5a**)	78
 (**6**)	 (**6a**)	70
 (**7**)	 (**7a**)	72

[a] Reactions were monitored by TLC.
[b] Confirmed by IR, ^{1}H NMR and ^{13}C NMR.
[c] Isolated yields.

bearing electron-donating substituents underwent the reaction smoothly to afford products **2a**–**5a** in a slightly better yields than those **6** and **7** bearing electron-withdrawing substituents giving corresponding [1,2,4]-triazol-3-yl amines **6a** and **7a**. The structure of the product **4a** has been further confirmed by X-ray crystallographic analysis as shown in Fig. 2.

Since the formation of [1,2,4]-triazole is an addition–dehydration reaction, hence the effect of substituents in the phenyl ring is expected to play an important role on reaction rates and on product yields. It is evident from the product yields that 1,3-diphenyl thioureas substituted with electron-donating groups gave better yields as compared to the substrates having electron-withdrawing groups. This observation is consistent with the observation made by Chorev et al. using $Hg(OAc)_2$.[9]

Furthermore, we have found a direct correlation between regioselectivity with the pK_as of the parent amines attached to thioureas during the construction of various heterocycles and related transformations and have established a good correlation between them. Recently, an excellent agreement between the regioselective N-acylation and the pK_as of the precursor amines attached to thioureas has been found.[15a] For heterocycles originating from unsymmetrical thioureas having ring nitrogen and an exocyclic nitrogen it has been observed that the amine having lower pK_a is part of the heterocyclic nitrogen and amine having higher pK_a goes to exocyclic nitrogen. So far this has been confirmed during the regioselective synthesis of thiazole-2-imine [or

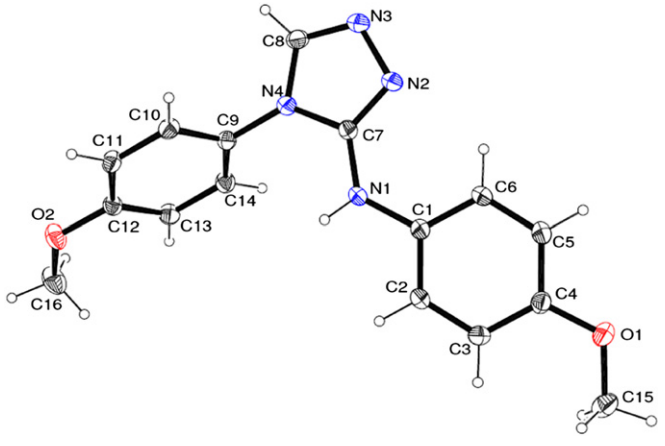
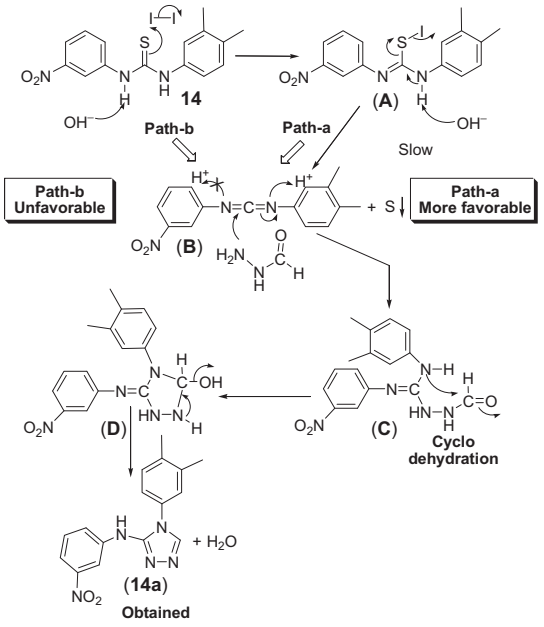


Fig. 2. Ortep view of compound **4a**.

2-iminothiazoline],[15b] 2-amino-4-thiazolidinones,[15c] thioamido guanidines[15d] and 1,5-disubstituted tetrazoles.[14e] We wanted to investigate whether the correlation of regioselectivity as a function of pK_a is applicable to the synthesis of [1,2,4]-triazol-3-yl-amine.

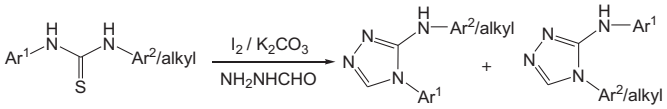
Although the mechanism proposed is essentially same as has been proposed by Chorev et al.[9] however with unsymmetrical thioureas the correlation between the regioselectivity with the pK_as of the parent amines is due to be ascertained. In the present methodology an excellent correlation between product regioselectivity and pK_a of the parent amines could be established, however, the effect due to steric factor of the substituents on the aryl ring of thiourea cannot be completely ruled out. As per the mechanism proposed in Scheme 1, the attack of the formic hydrazide (NH_2NHCHO) to the in situ generated unsymmetrical carbodiimide (**B**)[14d] would lead to an equilibrium where the protonation could occur towards either of the amino/imino nitrogen to afford carboximidamide. However, the equilibrium of protonation would be more favoured and shifted towards more basic nitrogen (path a, Scheme 1) to give the intermediate (**C**) rather than towards the less basic nitrogen atom (path b, Scheme 1). The carboximidamide (**C**) would then undergo an intramolecular nucleophilic attack from nitrogen atom onto the aldehydic carbonyl group to provide the intermediate (**D**). In a final step (**D**) undergoes a dehydration step to render the corresponding regioisomeric [1,2,4]-triazole. Thereby, nitrogen of the amine attached to the thiourea having higher pK_a should appear in the ring while the other amine would flank as an exocyclic nitrogen in the major product. As a typical illustration unsymmetrical thiourea **14** has been chosen, which exclusively gave **14a** and no trace of other regioisomer **14b** was obtained (Table 2). Structure of the regioselective product **14a** has been confirmed by crystal X-ray crystallography (Fig. 3).

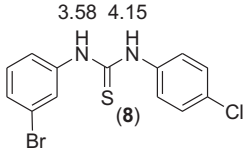
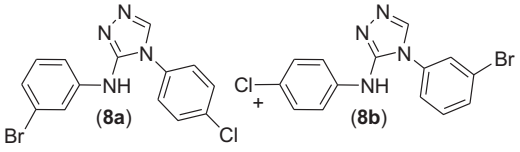
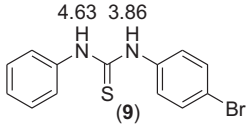
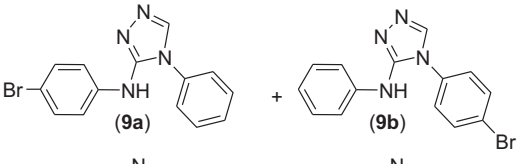
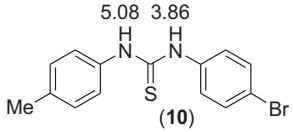
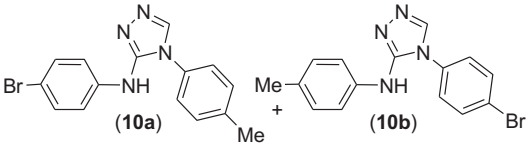
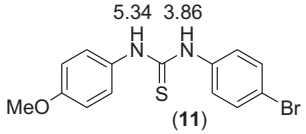
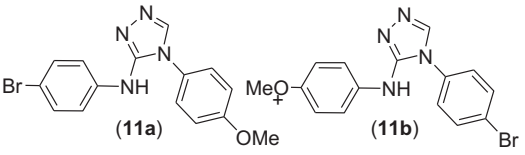


Scheme 1. Plausible mechanism for the regioselective formation of [1,2,4]-triazol-3-yl-amines.

Thus, it is expected, smaller the difference in pK_as of precursor amines attached to a thiourea, lesser should be the regioselectivity giving both the regioisomers because of the probability of protonation to either of the nitrogen atoms. A larger pK_a difference should yield exclusively one of the regioisomer due to the

Table 2
Formation of [1,2,4]-triazol-3-yl-amine from unsymmetrical thioureas[a]



Substrate[b]	(pK_a2−pK_a1)[c]	Product(s)[d]	% Yield[e] (ratio)[f]
 (**8**)	0.57	 (**8a**) + (**8b**)	80 (52:48)
 (**9**)	0.77	 (**9a**) + (**9b**)	72 (57:43)
 (**10**)	1.22	 (**10a**) + (**10b**)	77 (78:22)
 (**11**)	1.48	 (**11a**) + (**11b**)	70 (87:13)

(*continued on next page*)

Table 2 (*continued*)

Substrate[b]	(pK_a2-pK_a1)[c]	Product(s)[d]	% Yield[e] (ratio)[f]
3.52 5.08 (**12**)	1.56	(**12a**) + (**12b**)	73 (95:5)
2.15 4.52 (**13**)	2.37	(**13a**) + (**13b**)	60 (98:2)
2.46 5.28 (**14**)	2.82	(**14a**) + (**14b**)	70 (99:1)
3.86 10.66 (**15**)	6.80	(**15a**) + (**15b**)	52 (100:0)
3.92 10.78 (**16**)	6.86	(**16a**) + (**16b**)	62 (100:0)
2.46 10.78 (**17**)	8.32	(**17a**) + (**17b**)	55 (100:0)

[a] Reactions were monitored by TLC.
[b] pK_a of the parent amines.
[c] Dissociation constants of organic acids and bases. http://www.zirchrom.com/organic.htm.
[d] Confirmed by IR, ^1H NMR and ^{13}C NMR.
[e] Isolated yields.
[f] Ratio determined by ^1H NMR and/or HPLC.

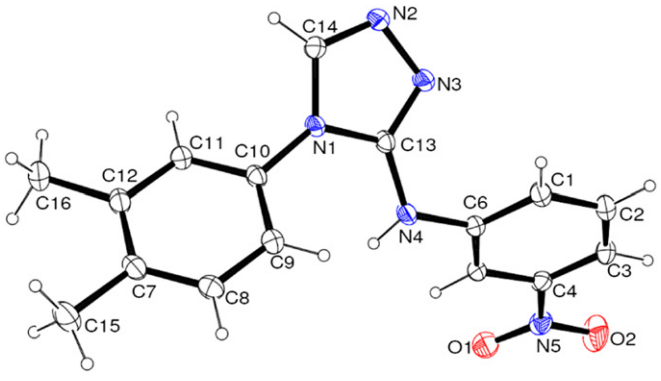


Fig. 3. Ortep view of compound **14a**.

preferential protonation towards one of the nitrogen during the formation of [1,2,4]-triazol-3-yl-amines. Hence a proper tuning of the pK_a would be useful to selectively form a single regioisomer. As a further proof to our hypothesis, various unsymmetrical thioureas were subjected to the present reaction condition with pK_a differences (pK_a2-pK_a1) ranging from 0.57 to 8.32 units. For instance, the unsymmetrical thiourea **8** containing *m*-bromo aniline and *p*-chloro aniline under the optimized reaction condition furnished a mixture of triazoles **8a** and **8b** in the ratio of 52:48. The measured pK_a of *m*-bromo aniline and *p*-chloro anilines are 3.58 and 4.15, respectively, a difference of 0.57 units (Table 2). Thus, as per our proposition, the formation of the major regioisomer **8a** satisfies this. The assumption of better regioselectivity with increase in the pK_a difference has been further demonstrated with other thioureas **9** and **10** having a pK_a difference of 0.77 and 1.22 units, respectively. There is an improvement in the regioselectivity with increase in pK_a

differences giving a pair of regioisomers **9a**/**9b** and **10a**/**10b** in the ratio of (57:43) and (78:22), respectively. When the pK_a difference rose from 1.48 to 1.56, the regioisomeric ratio further improved from 87:13 to 95:5 for the regioisomeric pairs **11a**/**11b** and **12a**/**12b** derived, respectively, from substrates **11** and **12**. When the difference in pK_as of the parent amine is above two pK_a units the ratio improved dramatically as demonstrated for substrates **13** and **14** giving regioisomers **13a**/**13b** and **14a**/**14b** in the ratio of 98:2 and 99:1, where the pK_a differences are 2.37 and 2.82, respectively. Beyond a pK_a difference of 1.8 or so exclusively one of the regioisomer was obtained. Substrates **15**, **16** and **17** having a pK_a difference of above 2.8 units gave regioisomers **15a**, **16a** and **17a** entirely and no traces of **15b**, **16b** and **17b** regioisomers could be detected. Structure of the regioisomer **17a** has been confirmed by crystal X-ray crystallography as shown in Fig. 4.

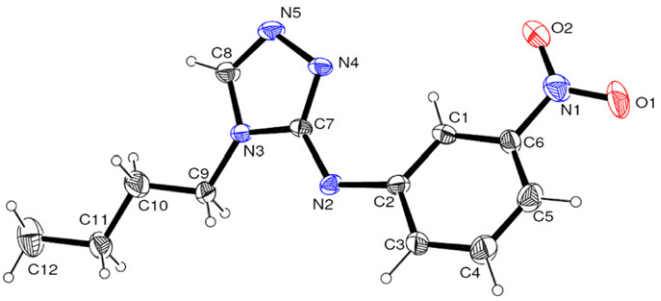


Fig. 4. Ortep view of compound **17a**.

A plot of the percentage of major regioisomers against pK_a differences revealed almost a linear correlation in the lower pK_a difference range as shown in Fig. 5. As the pK_a difference increases beyond 1.7, the change becomes abrupt and the linear correlation does not fit well, giving a flattened curve thereby indicating exclusive formation of one of the regioisomer, which is shown graphically in Fig. 5.

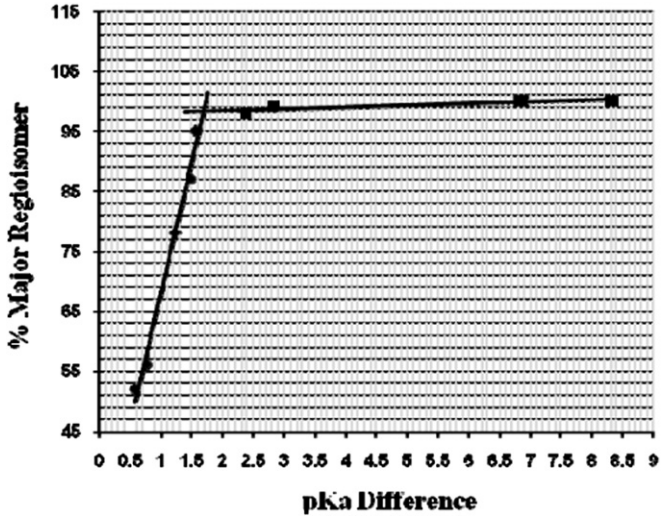


Fig. 5. A plot of pK_a difference and % of major regioisomer.

3. Conclusions

In conclusion we have developed a tandem one-pot method for the synthesis of 3-amino-[1,2,4]-triazoles from 1,3-disubstituted thioureas and NH_2NHCOR (R=H, Ph) using molecular iodine. For unsymmetrical thioureas the product regioselectivity correlates well with the pK_as of the parent amines in which the amine having lower pK_a stays as exocyclic nitrogen and the one having higher pK_a is part of the ring nitrogen. The methodology provides access to the formation of a single regioisomer through proper tuning of the pK_as of the parent amines in the unsymmetrical thioureas. In comparison to the reported methods, our method offers simple convenient approach for the construction of this pharmaceutically important heterocycle and thus has potential industrial application.

4. Experimental section

4.1. General remarks

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Reaction progress was monitored by TLC using silica gel 60 F_{254} (0.25 mm) with detection by UV or iodine. Chromatography was performed using silica gel (60–120 mesh size) with freshly distilled solvents. Columns were typically packed as slurry and equilibrated with the appropriate solvent system prior to use. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on FT-400 MHz instrument using TMS as an internal standard. Data are presented as follows: chemical shift (ppm), multiplicity (s=singlet, d=doublet, t=triplet, quin=quintet, m=multiplet, b=broad, br s=broad singlet, br m=broad multiplet, coupling constant *J* (Hz)). Elemental analyses were carried out on a Perkin–Elmer 2400 elemental analyzer and Euro Vector EA3000. Melting points were recorded and are uncorrected. IR spectra were recorded in KBr or neat. HPLC was performed using C-18 column.

4.2. General procedure for the preparation of *N*,4-disubstituted-4*H*-1,2,4-triazol-3-amine from symmetrical thioureas 1–7

To a suspension of 1,3-disubstituted thioureas **1**–**7** (1 mmol) in ethanol (2 mL) were added sequentially formic hydrazide (2.5 mmol) and aqueous K_2CO_3 (2.5 mmol in 0.5 mL water) and the mixture was stirred at room temperature. Under this stirring condition iodine (1.2 mmol) was added pinch wise over a period of 10 min. Disappearance of iodine colour was associated with the precipitation of colloidal sulfur. The reaction mixture was stirred for a further period of 20–40 min. During this period complete disappearance of 1,3-disubstituted thiourea was observed with the appearance of a new product having lower R_f. Precipitated elemental sulfur was filtered off and the filtrate ethanol was removed in a rotary evaporator. The reaction mixture was treated with a 5% hypo solution (5 mL) and the product was extracted with ethyl acetate (2×10 mL). The combined ethyl acetate layer was washed with water (1×5 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction product was purified over a column of silica gel and eluted with hexane/ethyl acetate mixture to give the corresponding products **1a**–**7a**.

*4.2.1. N,4-Diphenyl-4H-1,2,4-triazol-3-amine (**1a**).* The general procedure was followed. The product was purified by column chromatography (90% EtOAc/hexane) to give the title compound **1a** (191 mg, 81%) as yellowish white solid; R_f (90% EtOAc/hexane) 0.23; mp 213–216 °C; ν_{max} (KBr): 3448, 3222, 3052, 1598, 1550, 1496, 1388, 1255, 1198, 744 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ=8.38 (1H, s, –N=CH–N–), 7.50–7.60 (5H, m, Ar. C–H), 7.32 (2H, d, *J*=7.6 Hz, Ar. C–H), 7.23 (2H, t, *J*=8.4 Hz, Ar. C–H), 6.93 (1H, t, *J*=7.2 Hz, Ar. C–H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=150.9, 142.7, 142.5, 134.6, 131.4, 130.8, 130.2, 127.0, 123.0, 119.0 ppm; HRMS (ESI): MH^+, found 237.1132. $C_{14}H_{12}N_4$ requires 237.1135. Elemental analysis: found C, 71.12; H, 5.10; N, 23.79. $C_{14}H_{12}N_4$ requires C, 71.17; H, 5.12; N, 23.71%.

*4.2.2. N,4-Bis(p-tolyl)-4H-1,2,4-triazol-3-amine (**2a**).* The general procedure was followed. The product was purified by column chromatography (90% EtOAc/hexane) to give the title compound **2a** (219 mg, 83%) as white solid; R_f (90% EtOAc/hexane) 0.19; mp 224–226 °C; ν_{max} (KBr): 3434, 3224, 3175, 3122, 3007, 2957, 2919, 2857, 1610, 1586, 1552, 1513, 1383, 1258, 1196, 816, 808 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.31 (1H, s, −N═CH−N−), 7.38 (4H, d, J=2 Hz, Ar. C−H), 7.21 (2H, d, J=8.4 Hz, Ar. C−H), 7.06 (2H, d, J=8.0 Hz, Ar. C−H), 2.43 (3H, s, Ar−CH_3), 2.26 (3H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=151.3, 142.7, 141.3, 139.7, 132.7, 131.9, 131.5, 130.6, 126.8, 119.4, 21.4, 20.9 ppm; HRMS (ESI): MH^+, found 265.1454. $C_{16}H_{16}N_4$ requires 265.1448. Elemental analysis: found C, 72.72; H, 6.04; N, 21.26. $C_{16}H_{16}N_4$ requires C, 72.70; H, 6.10; N, 21.19%.

*4.2.3. N,4-Bis(3,4-dimethylphenyl)-4H-1,2,4-triazol-3-amine (**3a**).* The general procedure was followed. The product was purified by column chromatography (90% EtOAc/hexane) to give the title compound **3a** (219 mg, 75%) as white solid; R_f (90% EtOAc/hexane) 0.21; mp 173–175 °C; ν_{max} (KBr): 3428, 3218, 3046, 2916, 1602, 1553, 1505, 1454, 1365, 1199, 1023, 1006, 880 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.26 (1H, s, −N═CH−N−), 7.31 (1H, d, J=8.0 Hz, Ar. C−H), 7.24 (1H, s, Ar. C−H), 7.17 (1H, d, J=8.0 Hz, Ar. C−H), 7.12 (1H, s, Ar. C−H), 7.04 (1H, d, J=8.0 Hz, Ar. C−H), 6.97 (1H, d, J=8.0 Hz, Ar. C−H), 2.32 (6H, s, 2×Ar−CH_3), 2.19 (3H, s, Ar−CH_3), 2.17 (3H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=153.1, 142.4, 140.2, 139.9, 139.8, 138.3, 132.2, 132.1, 131.3, 131.1, 127.7, 124.2, 120.8, 117.0, 20.2, 20.0, 19.7, 19.3 ppm; HRMS (ESI): MH^+ found 293.1758. $C_{18}H_{20}N_4$ requires 293.1761. Elemental analysis: found C, 73.91; H, 6.87; N, 19.22. $C_{18}H_{20}N_4$ requires C, 73.94; H, 6.89; N, 19.16%.

*4.2.4. N,4-Bis(4-methoxyphenyl)-4H-1,2,4-triazol-3-amine (**4a**).* The general procedure was followed. The product was purified by column chromatography (100% EtOAc) to give the title compound **4a** (237 mg, 80%) as white crystalline solid; R_f (100% EtOAc) 0.26; mp 189–191 °C; ν_{max} (KBr): 3292, 3136, 2922, 2835, 1601, 1561, 1513, 1303, 1257, 1236, 1222, 1191, 1175, 1038, 1027, 840, 826 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.23 (1H, s, −N═CH−N−), 7.41 (2H, d, J=8.8 Hz, Ar. C−H), 7.28 (2H, d, J=8.8 Hz, Ar. C−H), 7.11 (2H, d, J=8.8 Hz, Ar. C−H), 6.83 (2H, d, J=9.2 Hz, Ar. C−H), 3.86 (3H, s, Ar−OMe), 3.75 (3H, s, Ar−OMe) ppm; ^{13}C NMR (100 MHz, CD_3OD+DMSO-d_6): δ=161.9, 156.4, 153.3, 142.7, 135.5, 128.8, 127.1, 121.3, 116.5, 115.5, 56.6, 56.3 ppm. Elemental analysis: found C, 64.89; H, 5.48; N, 18.83. $C_{16}H_{16}N_4O_2$ requires C, 64.85; H, 5.44; N, 18.91%.

*4.2.5. N,4-Bis(2-methoxyphenyl)-4H-1,2,4-triazol-3-amine (**5a**).* The general procedure was followed. The product was purified by column chromatography (90% EtOAc/hexane) to give the title compound **5a** (231 mg, 78%) as white solid; R_f (90% EtOAc/hexane) 0.21; mp 149–151 °C; ν_{max} (KBr): 3388, 3106, 2924, 2841, 1605, 1569, 1494, 1464, 1385, 1285, 1246, 1115, 1021, 988, 755 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.30 (1H, s, −N═CH−N−), 7.81 (1H, m, Ar. C−H), 7.58 (1H, t, J=8.0 Hz, Ar. C−H), 7.43 (1H, d, J=7.6 Hz, Ar. C−H), 7.32 (1H, d, J=8.4 Hz, Ar. C−H), 7.16 (1H, t, J=8.0 Hz, Ar. C−H), 6.92 (3H, m, Ar. C−H), 3.92 (3H, s, Ar−OMe), 3.81 (3H, s, Ar−OMe) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=155.3, 152.4, 149.2, 142.8, 133.0, 130.6, 129.1, 123.2, 122.9, 122.4, 122.1, 118.1, 114.1, 111.6, 56.9, 56.6 ppm. Elemental analysis: found C, 64.79; H, 5.51; N, 18.83. $C_{16}H_{16}N_4O_2$ requires C, 64.85; H, 5.44; N, 18.91%.

*4.2.6. N,4-Bis(4-bromophenyl)-4H-1,2,4-triazol-3-amine (**6a**).* The general procedure was followed. The product was purified by column chromatography (80% EtOAc/hexane) to give the title compound **6a** (276 mg, 70%) as white solid; R_f (70% EtOAc/hexane) 0.21; mp 239–242 °C; ν_{max} (KBr): 3221, 3173, 3116, 3060, 3021, 2969, 2922, 1601, 1549, 1488, 1405, 1194, 1070, 1006, 835, 819 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.41 (1H, s, −N═CH−N−), 7.76 (2H, d, J=8.4 Hz, Ar. C−H), 7.46 (2H, d, J=8.4 Hz, Ar. C−H), 7.38 (2H, d, J=8.8 Hz, Ar. C−H), 7.31 (2H, d, J=8.8 Hz, Ar. C−H) ppm; ^{13}C NMR (100 MHz, CD_3OD+DMSO-d_6): δ=152.1, 143.2, 134.5, 133.7, 133.0, 129.1, 128.3, 124.4, 120.7, 141.9 ppm. Elemental analysis: found C, 42.69; H, 2.52; N, 14.17. $C_{14}H_{10}Br_2N_4$ requires C, 42.67; H, 2.56; N, 14.22%.

*4.2.7. N,4-Bis(3-chlorophenyl)-4H-1,2,4-triazol-3-amine (**7a**).* The general procedure was followed. The product was purified by column chromatography (90% EtOAc/hexane) to give the title compound **7a** (219 mg, 72%) as white solid; R_f (70% EtOAc/hexane) 0.21; mp 196–198 °C; ν_{max} (KBr): 3433, 3230, 3116, 3060, 2960, 1592, 1552, 1480, 1378, 1226, 1197, 1096, 1077, 909, 793 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.44 (1H, s, −N═CH−N−), 7.64 (1H, s, Ar. C−H), 7.57 (2H, m, Ar. C−H), 7.47 (2H, m, Ar. C−H), 7.19–7.26 (2H, m, Ar. C−H), 6.93 (1H, m, Ar. C−H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=152.0, 143.9, 142.9, 136.8, 135.9, 135.7, 132.7, 131.4, 131.1, 127.4, 125.6, 122.7, 118.6, 117.0 ppm; HRMS (ESI): MH^+, found 305.0352. $C_{14}H_{10}Cl_2N_4$ requires 305.0355. Elemental analysis: found C, 55.06, H, 3.34, N, 18.42. $C_{14}H_{10}N_4Cl_2$ requires C, 55.10, H, 3.30, N, 18.36%.

4.3. General procedure for the preparation and determination of regioisomeric of *N*,4-disubstituted-4*H*-1,2,4-triazol-3-amine from unsymmetrical thioureas 8–17

For unsymmetrical thioureas (**8**–**17**) possessing two different aryl amines, the reaction and work up procedures were exactly the same as followed for symmetrical thiourea (**1**). However after work up the crude reaction mixture containing both the inseparable regioisomers (**8a**,**b**–**14a**,**b**) was purified over a column of silica gel and eluted as an inseparable mixture to get rid of the minor upper impurities that formed in the reaction. Fractions containing regioisomers were collected, combined, evaporated and were then subjected to ^1H NMR, ^{13}C NMR and HPLC analysis in order to determine their ratio in the reaction product.

*4.3.1. N-(3-Bromophenyl)-4-(4-chlorophenyl)-4H-1,2,4-triazol-3-amine (**8a**)+4-(3-bromophenyl)-N-(4-chlorophenyl)-4H-1,2,4-triazol-3-amine (**8b**).* The general procedure for the unsymmetrical thiourea was followed. The crude reaction mixture containing both the inseparable regioisomeric products (checked by TLC) was purified by column chromatography (80% EtOAc/hexane) to give the mixture of regioisomers **8a** and **8b** (280 mg, 80%) as white solid in the ratio of 52:48; R_f (70% EtOAc/hexane) 0.30; ν_{max} (KBr): 3234, 3023, 2965, 2970, 2922, 2850, 1608, 1555, 1491, 1437, 1410, 1383, 1195, 1092, 1010, 892, 833, 779 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.79 (s, −NH−), 8.77 (s, −NH−), 8.504 (s, −N═CH−N−), 8.499 (s, −N═CH−N−), 7.83 (s, Ar. C−H), 7.72–7.75 (m, Ar. C−H), 7.67 (s, Ar. C−H), 7.65 (s, Ar. C−H), 7.50–7.58 (m, Ar. C−H), 7.43 (d, J=8 Hz, Ar. C−H), 7.28 (d, J=9.2 Hz, Ar. C−H), 7.19 (t, J=8 Hz, Ar. C−H), 7.04 (d, J=8.8 Hz, Ar. C−H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ=149.7, 143.2, 141.4, 140.6, 134.5, 133.8, 131.9, 131.8, 130.7, 130.0, 128.6, 127.8, 124.9, 124.2, 123.1, 122.3, 121.9, 119.1, 118.6, 115.8 ppm; MS (ESI): MH^+, found 351.0. $C_{14}H_{10}BrClN_4$ requires 350.6.

*4.3.2. N-(4-Bromophenyl)-4-phenyl-4H-1,2,4-triazol-3-amine (**9a**)+4-(4-bromophenyl)-N-phenyl-4H-1,2,4-triazol-3-amine (**9b**).* The general procedure for the unsymmetrical thiourea was followed. The crude reaction mixture containing both the inseparable regioisomeric products as indicated by TLC was purified by column chromatography (90% EtOAc/hexane) to give the mixture of regioisomers **9a** and **9b** (227 mg, 72%) as white solid in the ratio of

57:43; R_f (70% EtOAc/hexane) 0.25; ν_{max} (KBr): 3444, 3220, 3176, 3115, 2966, 2922, 1600, 1548, 1407, 1491, 1383, 1315, 1230, 1197, 1070, 1007, 959, 826, 750 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.370 (s, −N═CH−N−), 8.366 (s, −N═CH−N−), 7.72 (d, J=8.8 Hz, Ar. C−H), 7.54–7.59 (m, Ar. C−H), 7.47–7.51 (m, Ar. C−H), 7.44 (d, J=8 Hz, Ar. C−H), 7.29–7.36 (m, Ar. C−H), 7.23 (t, J=8 Hz, Ar. C−H), 6.93 (t, J=7.2 Hz, Ar. C−H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ=150.0, 149.7, 141.6, 141.2, 133.2, 132.8, 132.6, 131.4, 129.9, 129.0, 128.7, 127.8, 125.5, 121.9, 120.5, 118.8, 116.8, 111.7 ppm; MS (ESI): MH^+, found 316.0. $C_{14}H_{11}BrN_4$ requires 316.1.

*4.3.3. N-(4-Bromophenyl)-4-p-tolyl-4H-1,2,4-triazol-3-amine (**10a**)+4-(4-bromophenyl)-N-p-tolyl-4H-1,2,4-triazol-3-amine (**10b**).* The general procedure for the unsymmetrical thiourea was followed. The crude reaction mixture containing both the inseparable regioisomeric products (checked by TLC) was purified by column chromatography (90% EtOAc/hexane) to give the mixture of regioisomers **10a** and **10b** (253 mg, 77%) as white solid in the ratio of 78:22; R_f (70% EtOAc/hexane) 0.25; ν_{max} (KBr): 3226, 3033, 1601, 1551, 1513, 1489, 1411, 1381, 1227, 1194, 1071, 1006, 957, 820 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.65 (s, −NH−), 8.44 (s, N−CH═N−), 8.41 (s, N−CH═N−), 7.77 (d, J=8.4 Hz, Ar. C−H), 7.44–7.50 (m, Ar. C−H), 7.34–7.39 (m, Ar. C−H), 7.03 (d, J=8 Hz, Ar. C−H), 2.38 (s, Ar−CH_3), 2.21 (s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ=149.9, 141.6, 141.3, 139.1, 138.8, 132.9, 131.4, 130.4, 129.4, 129.2, 127.8, 125.5, 122.0, 118.8, 117.1, 111.7, 20.8, 20.4 ppm; MS (ESI): MH^+, found 329.1. $C_{15}H_{13}BrN_4$ requires 329.1.

*4.3.4. N-(4-Bromophenyl)-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-amine (**11a**)+4-(4-bromophenyl)-N-(4-methoxyphenyl)-4H-1,2,4-triazol-3-amine (**11b**).* The general procedure for the unsymmetrical thiourea was followed. The crude reaction mixture containing both the inseparable regioisomeric products (checked by TLC) was purified by column chromatography (90% EtOAc/hexane) to give the mixture of regioisomers **11a** and **11b** (242 mg, 70%) as brown solid in the ratio of (87:13); R_f (90% EtOAc/hexane) 0.20; ν_{max} (KBr): 3242, 3055, 2924, 2852, 1601, 1553, 1512, 1492, 1299, 1244, 1196, 1179, 1111, 1073, 1031, 1001, 959, 829 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.62 (s, −NH−), 8.39 (s, −N═CH−N−), 8.34 (s, −N═CH−N−), 7.77 (d, J=8 Hz, Ar. C−H), 7.37–7.50 (m, Ar. C−H), 7.11 (d, J=8 Hz, Ar. C−H), 6.83 (d, J=8 Hz, Ar. C−H), 3.82 (s, Ar−OMe), 3.69 (s, Ar−OMe) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ=159.5, 153.6, 150.0, 141.5, 141.1, 134.7, 132.7, 132.6, 131.2, 127.8, 127.2, 125.7, 121.7, 118.6, 114.9, 113.9, 111.4, 55.5, 55.2 ppm; MS (ESI): MH^+, found 346.1. $C_{15}H_{13}BrN_4O$ requires 346.1.

*4.3.5. N-(3-Chlorophenyl)-4-p-tolyl-4H-1,2,4-triazol-3-amine (**12a**)+4-(3-chlorophenyl)-N-p-tolyl-4H-1,2,4-triazol-3-amine (**12b**).* The general procedure for the unsymmetrical thiourea was followed. The crude reaction mixture containing both the inseparable regioisomeric products (checked by TLC) was purified by column chromatography (90% EtOAc/hexane) to give the mixture of regioisomers **12a** and **12b** (208 mg, 73%) as white solid in the ratio of (95:5); R_f (70% EtOAc/hexane) 0.33; ν_{max} (KBr): 3726, 3216, 3130, 3010, 2921, 2852, 1599, 1554, 1513, 1481, 1383, 1197, 1097, 906, 819, 771, 670 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=8.74 (s, −NH−), 8.45 (s, −N═CH−N−), 7.68 (s, Ar. C−H), 7.39 (s, Ar. C−H), 7.23 (t, J=8 Hz, Ar. C−H), 6.89 (d, J=8 Hz, Ar. C−H), 2.38 (s, Ar−CH_3), 2.21 (s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ=149.5, 143.2, 141.5, 138.6, 133.1, 130.4, 130.2, 125.4, 119.8, 116.0, 115.1, 20.6 ppm; MS (ESI): MH^+, found 285.5. $C_{15}H_{13}ClN_4$ requires 285.7.

*4.3.6. N-(3,5-Bis(trifluoromethyl)phenyl)-4-(2-methoxyphenyl)-4H-1,2,4-triazol-3-amine (**13a**)+4-(3,5-bis(trifluoromethyl)phenyl)-N-(2-methoxyphenyl)-4H-1,2,4-triazol-3-amine (**13b**).* The general procedure for the unsymmetrical thiourea was followed. The crude reaction mixture containing both the inseparable regioisomeric products (checked by TLC) was purified by column chromatography (80% EtOAc/hexane) to give the mixture of regioisomers **13a** and **13b** (241 mg, 60%) as white solid in the ratio of (98:2); R_f (70% EtOAc/hexane) 0.24; ν_{max} (KBr): 3262, 3228, 3096, 2967, 1679, 1598, 1562, 1508, 1475, 1386, 1278, 1185, 1121, 1022, 944, 878, 755, 681 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=9.19 (s, −NH−), 8.38 (s, −N═CH−N−), 8.06 (s, −N═CH−N−), 6.89–7.60 (br m, Ar. C−H), 3.77 (s, Ar−OMe) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=169.6, 162.5, 156.4, 152.2, 143.8, 133.3, 129.7, 128.1, 127.2, 122.5, 121.4, 117.9, 114.8, 114.0, 112.6, 56.5 ppm; MS (ESI): MH^+, found 403.2. $C_{17}H_{12}F_6N_4O$ requires 403.2.

*4.3.7. 4-(3,4-Dimethylphenyl)-N-(3-nitrophenyl)-4H-1,2,4-triazol-3-amine (**14a**)+N-(3,4-dimethylphenyl)-4-(3-nitrophenyl)-4H-1,2,4-triazol-3-amine (**14b**).* The general procedure for the unsymmetrical thiourea was followed. The crude reaction mixture containing both the inseparable regioisomeric products (checked by TLC) was purified by column chromatography (90% EtOAc/hexane) to give the mixture of regioisomers **14a** and **14b** (216 mg, 70%) as yellow solid in the ratio of (99:1 or ~100% **14a**); R_f (90% EtOAc/hexane) 0.22; ν_{max} (KBr): 3443, 3214, 3178, 2921, 1605, 1548, 1525, 1295, 1251, 1234, 1196, 1020, 872, 817, 736, 667 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ=9.10 (1H, s, −NH−), 8.57 (1H, s, −N═CH−N−), 8.46 (1H, s, Ar. C−H), 7.97 (1H, d, J=8 Hz, Ar. C−H), 7.71 (1H, d, J=8 Hz, Ar. C−H), 7.52 (1H, t, J=8 Hz, Ar. C−H), 7.36 (1H, s, Ar. C−H), 7.33 (1H, d, J=4.8 Hz, Ar. C−H), 7.24 (1H, d, J=8 Hz, Ar. C−H), 2.299 (3H, s, Ar−CH_3), 2.290 (3H, s, Ar−CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD+DMSO-d_6): δ=151.5, 150.3, 144.0, 143.8, 140.2, 139.9, 132.3, 131.9, 131.2, 128.1, 124.5, 124.4, 116.8, 112.9, 20.2, 19.9 ppm; MS (ESI): MH^+, found 310.2. $C_{16}H_{15}N_5O_2$ requires 310.3.

*4.3.8. N-(4-Bromophenyl)-4-cyclohexyl-4H-1,2,4-triazol-3-amine (**15a**).* The general procedure for the unsymmetrical thiourea was followed. The crude product containing single regioisomer (as indicated by TLC) was purified by column chromatography (100% EtOAc) to give the title compound **15a** (167 mg, 52%) as white solid; R_f (100% EtOAc) 0.21; mp 197–200 °C; ν_{max} (KBr): 3301, 3188, 3138, 3086, 2925, 2853, 1606, 1552, 1488, 1238, 1203, 1003, 819 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.38 (1H, s, −N═CH−N−), 7.37 (2H, d, J=7.6 Hz, Ar. C−H), 7.27 (2H, d, J=7.6 Hz, Ar. C−H), 4.05 (1H, m, aliphatic C−H), 2.05 (2H, d, J=12.0 Hz, aliphatic C−H), 1.90 (2H, d, J=12.8 Hz, aliphatic C−H), 1.63–1.75 (4H, m, aliphatic C−H), 1.46 (2H, m, aliphatic C−H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=152.0, 142.5, 134.6, 133.1, 120.2, 114.6, 55.2, 34.6, 26.7, 26.2 ppm. Elemental analysis: found C, 52.39; H, 5.36; N, 17.46. $C_{14}H_{17}BrN_4$ requires C, 52.35; H, 5.33; N, 17.44%.

*4.3.9. 4-Butyl-N-(naphthalene-1yl)-4H-1,2,4-triazol-3-amine (**16a**).* The general procedure for the unsymmetrical thiourea was followed. The crude product containing single regioisomer (as indicated by TLC) was purified by column chromatography (100% EtOAc) to give the title compound **16a** (166 mg, 62%) as black gum; R_f (100% EtOAc) 0.20; ν_{max} (KBr): 3054, 2958, 2927, 2856, 1629, 1557, 1463, 1403, 1274, 792, 772 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.32 (1H, s, −N−CH═N−), 8.09 (1H, m, Ar. C−H), 7.86 (1H, m, Ar. C−H), 7.59 (1H, d, J=8.0 Hz, Ar. C−H), 7.49 (2H, m, Ar. C−H), 7.09 (1H, d, J=7.2 Hz, Ar. C−H), 3.91 (2H, t, J=7.2 Hz, aliphatic-CH_2−), 1.74 (2H, quin, J=7.6 Hz, aliphatic-CH_2−), 1.27 (2H, m, aliphatic-CH_2−), 0.86 (3H, t, J=7.2 Hz, aliphatic-CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=153.5, 142.3, 137.7, 134.9, 128.3, 127.2, 126.1, 125.71, 125.66, 123.6, 122.0, 115.9, 43.6, 31.3, 19.4, 12.6 ppm. Elemental analysis: found C, 72.19; H, 6.77; N, 21.06. $C_{16}H_{18}N_4$ requires C, 72.15; H, 6.81; N, 21.04%.

*4.3.10. 4-Butyl-N-(3-nitrophenyl)-4H-1,2,4-triazol-3-amine (**17a**).* The general procedure for the unsymmetrical thiourea was followed. The crude product containing single regioisomer (as

indicated by TLC) was purified by column chromatography (100% EtOAc) to give the title compound **17a** (144 mg, 55%) as yellow solid; R_f (100% EtOAc) 0.19; mp 127–130 °C; ν_{max} (KBr): 3252, 3142, 2961, 2930, 2851, 1630, 1613, 1553, 1531, 1353, 1251, 997, 853, 803, 739 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): δ=8.36 (2H, m, –N–CH=N– and Ar. C–H), 7.76–7.79 (2H, m, Ar. C–H), 7.50 (1H, t, J=8.0 Hz, Ar. C–H), 4.02 (2H, t, J=7.6, aliphatic-CH_2–), 1.78 (2H, quin, J=7.6 Hz, aliphatic-CH_2–), 1.37 (2H, sextet, J=7.6 Hz, aliphatic-CH_2–), 0.96 (3H, t, J=7.6 Hz, aliphatic-CH_3) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ=152.1, 150.5, 144.3, 143.2, 131.3, 123.9, 116.9, 112.5, 44.7, 33.0, 20.8, 14.0 ppm; HRMS (ESI): MH^+, found 262.1296. $C_{12}H_{15}N_5O_2$ requires 262.1299. Elemental analysis: found C, 55.19; H, 5.76; N, 26.83. $C_{12}H_{15}N_5O_2$ requires C, 55.16; H, 5.79; N, 26.80%.

4.4. Crystallographic description

Crystal data were collected with a Bruker Smart Apex-II CCD diffractometer by using graphite monochromated MoKα radiation (λ=0.71073 Å) at 298 K. Cell parameters were retrieved using SMART[16] software and refined with SAINT[16] on all observed reflections. Data reduction was performed with the SAINT software and corrected for Lorentz and polarization effects. Absorption corrections were applied with the program SADABS.[17] The structure was solved by direct methods implemented in SHELX-97[18] program and refined by full-matrix least-squares methods on F^2. All non-hydrogen atomic positions were located in difference Fourier maps and refined anisotropically. The hydrogen atoms were placed in their geometrically generated positions. All the crystals were isolated in rectangular shape from ethyl acetate and hexane mixture at room temperature. CCDC numbers for compounds **4a**, **14a** and **17a** are CCDC-824581, CCDC-831538 and CCDC-824582, respectively. These data can be obtained from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Supplementary data

X-ray crystallographic data (CIF file) of **4a, 14a** and **17a** as well as copies of ^1H and ^{13}C NMR and HRMS spectra of products. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.04.042.

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