Organic & Biomolecular Chemistry

Dynamic Article Links

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 8422

www.rsc.org/obc

PAPER

An efficient strategy for the general synthesis of 3-aryl substituted pyrazolo[5,1-*c*][1,4]benzoxazines and pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones†‡

Kaushik Brahma,§ Anup Kumar Sasmal§ and Chinmay Chowdhury*

Received 9th August 2011, Accepted 6th September 2011
DOI: 10.1039/c1ob06353g

An efficient strategy for the general synthesis of 3-aryl substituted pyrazolo[5,1-*c*][1,4]benzoxazines and pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones has been developed using intramolecular 1,3-dipolar cycloaddition. The hydrazonoyl chloride, the precursor of the cycloadduct, is accessed easily through a two-step reaction carried out in one-pot. It is then used without purification for the base induced formation of the nitrilimine, which undergoes subsequent *in situ* intramolecular cycloaddition with an alkyne to afford the desired product. The reaction protocol has also been applied in bis-heteroannulation and in the synthesis of uracil derivatives of biological interest. The operational simplicity of the process, the use of cheap starting materials, and the relatively short reaction times required make the process convenient and practical.

Introduction

1,4-Benzoxazines have attracted considerable interest in recent times because of their presence as a key structural component in numerous biological and therapeutic compounds. Notable examples are *actinomycin D* – an anticancer drug isolated from *Streptomyces*,[1a] *C-1027* – a potent antitumor chromprotein isolated from *Streptomyces globisporus* C-1027,[1b] and benzoxazinorifamycin *KRM-1648* known for antitubercular activities,[1c] besides *flumioxazin* and *thidiazimin* used as herbicides.[1d] Additionally, tricyclic pyrazolo-benzoxazines have been described as inhibitors of mitotic kinesin[2a] and viral replications[2b] in recent patents, while imidazolo-benzoxazines have been identified as modulators of 5-HT1 receptors.[2c] Parallel to this, 1,4-benzodiazepin-5-ones are considered to constitute a privileged structure in medicinal chemistry[3] as they hit various pharmacologically significant targets (*e.g.*, enzymes, ion channels, GPCRs *etc.*). Thus this class of compounds has been well recognised for the broad range of activities such as anti-tumor,[4a] anti-depressant,[4b] anti-insectan,[4c] analgesic,[4d] fibrinogenic receptor antagonist,[4e] *etc*. The range of their therapeutic activities has been increased further through development of scaffolds *via* fusion with different nitrogen heterocycles (*e.g.*, imidazole, triazole, oxazole, pyrimidine *etc.*). For example, flumazenil[5] **1** is used as an antihistaminic compound, while bretazenil[6] **2** is popular for its potential use against neurodegenerative diseases (Fig. 1).

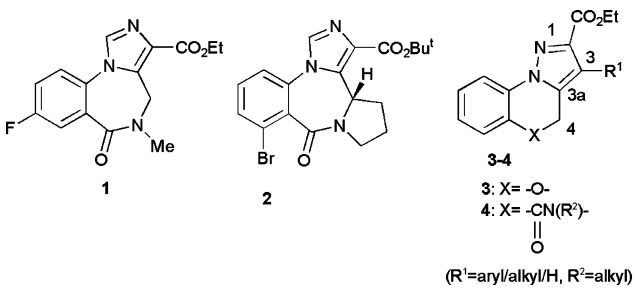


Fig. 1 Some important fused 1,4-benzodiazepin-5-ones and analogues.

Though there are many synthetic approaches towards 1,4-benzoxazines,[7] 1,4-benzodiazepin-5-ones,[8] and pyrazoles,[9] only few synthetic methods are available for pyrazoles fused with 1,4-benzoxazine[10] or 1,4-benzodiazepinone.[11] Garanti *et al.* reported the synthesis of 2-substituted 4*H*-pyrazolo[5,1-*c*][1,4]benzoxazines[10a] from 1-nitro- and 1-phenylsulfonyl-*N*-[2-(2-propynyloxy)phenyl]hydrazones through the intramolecular cycloaddition of nitrilimines with terminal alkynes. The same group reported the synthesis of 2-carbethoxy-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazines **3** (R^1 = H/Ph) based on nitrilimine cycloaddition utilising substituted ethylenes[10b] and acetylenes[10c] as dipolarophiles. However, both of the approaches involved harsh reaction conditions like prolonged heating (up to 108 h). In addition, only one 3-substituted derivative (R^1 = Ph) of pyrazolo[5,1-*c*][1,4]benzoxazine **3** was reported,[10b–c] demonstrating that the methodologies lacked generality. Recently,

Chemistry Division, Indian Institute of Chemical Biology (CSIR), 4, Raja S. C. Mullick Road, Kolkata-700032, India. E-mail: chinmay@iicb.res.in

† Dedicated to Prof. Nitya. G. Kundu on the occasion of his 75th birth anniversary.

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterisation data and NMR spectra. CCDC reference number 838046. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob06353g

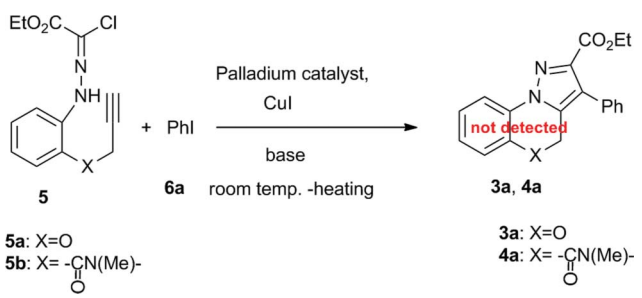
§ Contributed equally.

a synthetic method for pyrido-/quinolino-fused pyrazolo[5,1-*c*][1,3]benzoxazines has been reported.[12] On the other hand, pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones[11a] **4** (R^1 = H, R^2 = Me) and the corresponding optically active 3,3a-dihydro analogues[13] were synthesised adopting the strategy of intramolecular cycloaddition of nitrilimines with substituted ethylenes. To the best of our knowledge, there is no report about the synthesis of 3-substituted derivatives of **4**. Therefore, there is an urgent need for a general, convenient and practical method for the synthesis of 3-substituted pyrazolo[5,1-*c*][1,4]benzoxazines **3** and pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones **4**.

The strategy adopted for the synthesis of targeted compounds **3**, **4** had its origin in our recent successful efforts for the synthesis of 1,2,3-triazoles fused with various heterocycles such as isoindoline,[14a] morpholine,[14b] 1,4-benzoxazine,[14c] 1,4-benzodiazepin-5-one,[14d] 1,5-benzodiazocin-6-one[14d] and piperazine[14e] using the intramolecular cycloaddition of azide with suitably designed alkynes. We realised that the azide can be replaced as the 1,3-dipole by a nitrilimine, which has been applied popularly in the synthesis of different azole derivatives.[15] With this in mind, we attempted to explore the potential of the intramolecular cycloaddition of nitrilimines with alkynes, culminating in the general synthesis of 3-substituted pyrazolo-1,4-benzoxazine/[1,4]benzodiazepin-6(4*H*)-ones **3**/**4**. We describe herein the results obtained in this attempt.

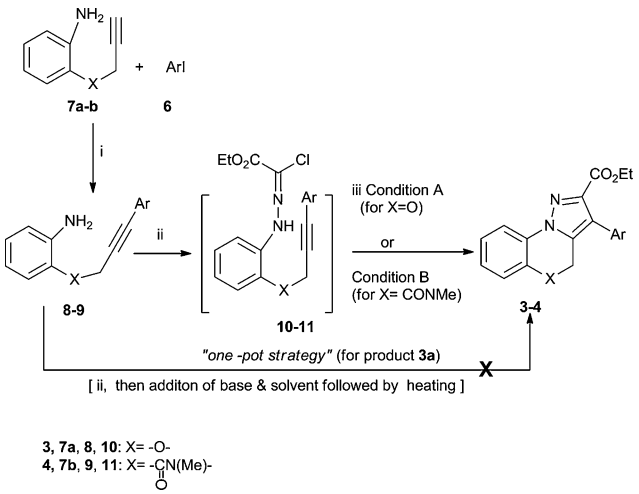
Results and discussion

At the outset, we chose to use propargylated hydrazonoyl chlorides **5a–b** as substrates. We anticipated that substrate **5a** (or **5b**) could undergo palladium catalysed C-arylation at the terminal alkyne with initial base induced formation of nitrilimine followed by *in situ* intramolecular cycloaddition, leading to the targeted product **3** (or **4**) in one pot (Scheme 1). To assess the idea, we initiated a model study of the reaction between **5a** and phenyl iodide **6a** under various reaction conditions employing copper(I) iodide, palladium catalyst [*e.g.*, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2/PPh_3$, $Pd(PPh_3)_4$, $PdCl_2/PPh_3$, Pd-C/PPh_3, *etc.*] and base [*e.g.*, Et_3N, piperidine, pyridine, K_2CO_3/Bu_4NBr, Cs_2CO_3/Bu_4NBr *etc.*]. To our surprise, these merely culminated in the polymerisation of substrates leading to tarry products, furnishing (in few cases) the C-phenylated product at the terminal alkyne (of **5a**) in low yields (10–15%). Replacing the substrate **5a** by **5b** also did not improve the situation as neither the product **4a** was formed nor did the starting materials survive.



Scheme 1 Attempted synthesis of products **3a** and **4a**.

The results prompted us to find an alternative "*one-pot strategy*" as depicted under Scheme 2. Thus, 2-(3-phenylprop-2-ynyloxy)aniline **8a** (Ar = Ph), prepared in turn from amine **7a** by palladium catalysed Sonogashira reaction,[16] was allowed to undergo diazotisation and subsequent Japp–Klingemann reaction[17] using ethyl 2-chloroacetoacetate followed by heating at 100 °C or higher temperature (adding a high-boiling solvent) in the presence of excess amounts of different types of bases. Once again no sign of the formation of any product **3a** was observed; only a tarry product was encountered. In this context, it is noteworthy that smooth conversion to a transient intermediate species **10a** (Ar = Ph) was evident from TLC monitoring and product isolation; however, subsequent heating to effect cycloaddition possibly triggered the formation of a tarry material instead of the product. Therefore, we isolated the intermediate **10a** (Ar = Ph) from the reaction mixture as crude through standard work-up and then refluxed it in xylene in the presence of Et_3N (5.0 equiv.) as base. To our gratification, it underwent cycloaddition smoothly within 6 h, affording the product **3a** with 49% yield starting from substrate **8a**. We then decided to pursue this strategy for the general synthesis of **3,4** with slight modification (discussed below) in the cycloaddition step to reduce the reaction times and enhance the yields as well.



Scheme 2 Synthesis of the products **3–4**. *Reagents and conditions*: i) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, DMF (used only for product **9**), rt, 2–6 h; ii) a) $NaNO_2$, HCl, 0–5 °C, 1 h; then b) ethyl 2-chloroacetoacetate, rt, 4–5 h; iii) Condition A: NaOAc, Bu_4NBr, chlorobenzene, 135 °C, 20–60 min; Condition B: Et_3N, xylene, 140 °C, 2.5–4.0 h.

The requisite starting substrates **8a–l** could be derived *via* palladium catalysed reaction of 2-(prop-2-ynyloxy)aniline **7a** with a variety of aryl iodides **6a–l** at room temperature for few hours (Scheme 2). Next, diazotisation followed by Japp–Klingemann reaction could be smoothly conducted in one pot, affording the intermediate **10**, the precursor compound of cycloadduct **3**. To find out the optimised reaction conditions for cycloaddition, we tested the cycloaddition of crude intermediate **10a** (Ar = Ph) by varying the solvents and bases (for details see screening studies in the ESI‡). Pleasingly, we observed that cycloaddition affording the product **3a** (53%) could be completed within 30 min only, through the employment of sodium acetate (4.0 equiv.) and Bu_4NBr (10 mol%) in chlorobenzene under reflux (condition A, Scheme 2). Next we used these optimised reaction conditions

for the synthesis of products **3b–l** (Table 1). Various functional groups including both electron donating (*e.g.*, OMe, Me) and electron withdrawing (*e.g.*, CO_2Me, NO_2, F, CF_3) types were well tolerated. The electron withdrawing functional groups in the aryl moiety (**6** and **8**) afforded higher yields compared to electron donating groups in both Sonogashira and cycloaddition reactions (Table 1, entries 6, 7, 10, 11 *vs.* 5, 8). Cycloadditions were usually found to be complete within 20–30 min only (except entry 8, Table 1). Interestingly, when the dialkynyl compound **8l** (derived from Sonogashira reaction using 1,2-diiodobenzene **6l**) was submitted to this reaction, a bis-benzoxazinyl derivative **3l** was formed (Table 1, entry 12), indicating the process to be viable for polyheteroannulation reactions.

The above reaction could be applied to the synthesis of pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones **4** as well (Scheme 2 and Table 2). Accordingly, alkyne **9**, produced from substrate **7b** *via* palladium catalysed reaction, was subjected to one pot diazotisation and subsequent Japp–Klingemann reaction to access the intermediate **11** as per the earlier protocol. However, unlike the previous systems, use of Et_3N and xylene as base and solvent proved to be the best conditions in this case. Thus refluxing (138–140 °C) the crude intermediate **11** in xylene for few hours in the presence of Et_3N (6.0 equiv.) furnished the targeted product **4** with moderate yields. As can be seen from Table 2, various functional groups (*e.g.*, Me, OMe, F, NO_2) were found to be compatible with this reaction. Apparently, the electron donating substituents in the aryl moiety of intermediate **11** ensured slightly better yields of product **4** as compared to electron withdrawing groups (Table 2, entries 3, 4, 6 *vs.* 5, 8). In contrast to our earlier observations (Table 1), the time period for cycloaddition to give product **4** was somewhat higher, possibly because a seven membered product is formed.

The structures of the products **3,4** were well characterised by spectral (^1H and ^{13}C NMR, IR, and mass spectra) and analytical data. Single crystal X-ray diffraction analysis[18] of product **3j** lent further support to this (Fig. 2).‡

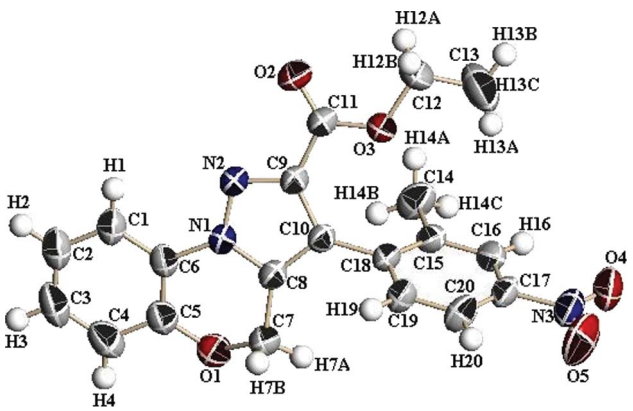
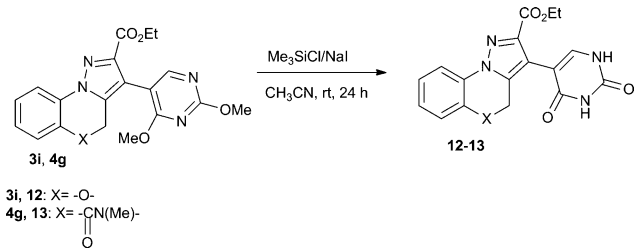


Fig. 2 ORTEP representation of product **3j**.

In view of the immense biological activities of 5-substituted uracils[19] and because of our own interest[20] in the development of bioactive molecules, some of the synthesised compounds were converted into novel uracil derivatives. When products **3i** and **4g** were treated separately with chlorotrimethylsilane and sodium iodide in dry acetonitrile at room temperature, a facile demethylation took place resulting in 5-substituted uracil derivatives **12** and **13**, respectively (Scheme 3). Thus, we have enlarged the scope of the reactions through the synthesis of novel uracil derivatives of potential biological interest.[21]



Scheme 3 Synthesis of uracil derivatives **12–13**.

Conclusion

In conclusion, we have disclosed an elegant strategy for the general synthesis of 3-substituted pyrazolo[5,1-*c*][1,4]benzoxazines and pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones. A wide variety of functionalised derivatives were synthesised. The intermediate hydrazonoyl chlorides, the precursor compounds of the cycloadduct, could easily be accessed through a two-step reaction carried out in one pot. The resulting crude product was used directly for the subsequent cycloaddition step. This reaction protocol has been applied for a bis-heteroannulation process also. The scope of this reaction has also been demonstrated by the synthesis of uracil derivatives of potential biological interest. The operational simplicity of the process, coupled with the use of cheap starting materials and relatively short reaction times makes the process convenient and practical. We believe that this reaction strategy may find application in library generation based on diversity oriented synthesis for lead development.

Experimental section

General procedure (condition A) for the synthesis of 3-aryl substituted pyrazolo[5, 1-*c*][1,4]benzoxazines 3

To an ice-cooled (0–5 °C) solution of **8** (0.85 mmol) in MeOH (1.5 mL), 6 M hydrochloric acid (0.5 mL) and $NaNO_2$ (117 mg, 1.70 mmol) were added successively, and the reaction mixture was allowed to stir at this temperature for one hour. The acidity of the medium was then adjusted to pH 5 by careful addition of sodium acetate. Next, a solution of ethyl 2-chloroacetoacetate (0.12 mL, 0.85 mmol) in MeOH (1 mL) was added dropwise and the mixture was allowed to stir vigorously at room temperature. After completion (4 h) of the reaction, the solvent was removed under reduced pressure and the residue was extracted with EtOAc (2 × 15 mL). The organic extracts were washed with saturated aqueous $NaHCO_3$ solution (15 mL) followed by water (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude intermediate **10** was then used directly. Thus, a solution of the product **10** in chlorobenzene (4 mL) was refluxed in the presence of NaOAc (278 mg, 3.40 mmol) and *n*-Bu_4NBr (27 mg, 0.08 mmol) until complete consumption of the starting material (TLC). After removal of the solvent, it was extracted with ethyl acetate (3 × 20 mL) and the combined

Table 1 Synthesis of pyrazolo[5,1-*c*][1,4]benzoxazines **3** through intermediate **8**

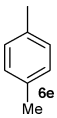
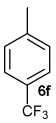
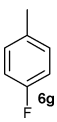
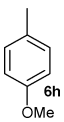
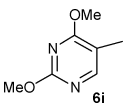
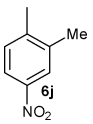
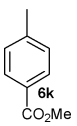
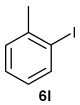
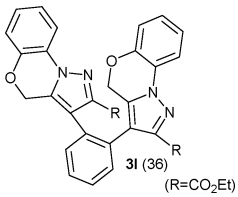
Entry	Aryl Iodide (**6**) Ar	Products[a] **8** (Yield%)[b]	Products[c] **3** (Yield%)[d]	Heating time	Overall[e] (Yield%)
1	 **6a**	**8a** (89)	**3a** (53)	30 min	47
2	 **6b**	**8b** (81)	**3b** (64)	30 min	52
3	 **6c**	**8c** (92)	**3c** (45)	30 min	41
4	 **6d**	**8d** (83)	**3d** (46)	20 min	38
5	 **6e**	**8e** (69)	**3e** (43)	20 min	30
6	 **6f**	**8f** (92)	**3f** (51)	20 min	47
7	 **6g**	**8g** (74)	**3g** (50)	25 min	37
8	 **6h**	**8h** (70)	**3h** (47)	1 h	33
9	 **6i**	**8i** (84)	**3i** (44)	25 min	37
10	 **6j**	**8j** (96)	**3j** (64)	30 min	61
11	 **6k**	**8k** (89)	**3k** (61)	30 min	54

Table 1 (*Contd.*)

Entry	Aryl Iodide (**6**) Ar	Products[a] **8** (Yield%)[b]	Products[c] **3** (Yield%)[d]	Heating time	Overall[e] (Yield%)
12	 **6l**	**8l** (51)	 **3l** (36) (R=CO_2Et)	20 min	18

[a] Reaction conditions: iodide **6** (1.0 mmol), acetylene **7a** (1.2 mmol), $Pd(PPh_3)_2Cl_2$ (0.03 mmol), CuI (0.05 mmol) in dry Et_3N (4 mL) stirred at rt for 2–6 h. [b] Chromatographically isolated pure products. [c] Reaction conditions: **8** (0.85 mmol) in methanol (1.5 mL), 6 M hydrochloric acid (0.5 mL), $NaNO_2$ (1.70 mmol) stirred at 0–5 °C for 1 h. After adjusting the pH of the reaction mixture to 5.0, ethyl 2-chloroacetoacetate (0.85 mmol) in MeOH (1 mL) was added and then stirred at rt for 4h. After usual work-up a crude product **10** was obtained. The crude product in chlorobenzene (4 mL) was heated under reflux in the presence of NaOAc (3.4 mmol) and Bu_4NBr (0.085 mmol). [d] Yields of isolated pure products based on the alkyne **8**. [e] Overall yield was calculated based on starting iodide **6**.

organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. Finally, the crude residue was purified by silica gel (100–200 mesh) column chromatography using 4–30% EtOAc in petroleum ether (v/v) as eluent.

2-Carbethoxy-3-phenyl-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine[10c] (3a). Yield: 53%; solid, m.p.: 114–116 °C (lit.[10c] 112 °C); IR (KBr): 2989, 1714, 1605, 1495, 1386, 1227, 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 5.24 (s, 2H), 7.08 (td, J = 1.2, 7.2 Hz, 1H), 7.14 (dd, J = 1.4, 7.7 Hz, 1H), 7.21 (td, J = 1.5, 7.7 Hz, 1H), 7.32–7.35 (m, 2H), 7.37–7.45 (m, 3H), 8.05 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 61.1, 62.1, 116.6, 117.5, 121.6, 122.8, 125.9, 127.66, 127.7, 128.1, 129.7, 130.3, 132.1, 141.7, 146.4, 162.1; ESI-MS: m/z 343.11 $[M+Na]^+$; HRMS (EI, 70 eV) calcd for $C_{19}H_{16}N_2O_3$ $[M^+]$ 320.1161, found 320.1158.

2-Carbethoxy-3-(naphthalene-1-yl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3b). Yield: 64%; solid, m.p.: 116–118 °C; IR (KBr): 2975, 1720, 1605, 1505, 1388, 1232, 1171, 1022 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 0.85 (t, J = 6.9 Hz, 3H), 4.05–4.13 (m, 2H), 5.06 (d, J = 13.8 Hz, 1H), 5.11 (d, J = 13.8 Hz, 1H) 7.07 (dd, J = 1.2, 8.4 Hz, 1H), 7.16 (td, J = 1.2, 7.8 Hz, 1H), 7.23 (td, J = 1.8, 7.8 Hz, 1H), 7.40 (dd, J = 1.2, 7.2 Hz, 1H), 7.42–7.45 (m, 1H), 7.48–7.54 (m, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 2H), 8.13 (dd, J = 1.8, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 13.5, 60.8, 62.2, 116.7, 117.6, 119.1, 122.9, 125.1, 125.3, 125.9, 126.0, 126.3, 127.8, 127.9, 128.2, 128.3, 128.5, 132.4, 133.1, 133.5, 143.4, 146.4, 161.8; HRMS (EI, 70 eV) calcd for $C_{23}H_{18}N_2O_3$ $[M^+]$ 370.1317, found 370.1310.

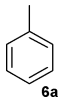
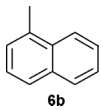
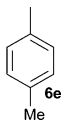
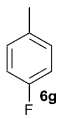
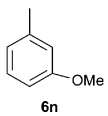
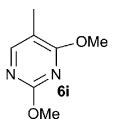
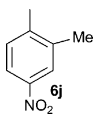
2-Carbethoxy-3-(4-fluorophenyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3g). Yield: 50%; solid, m.p.: 146–147 °C; IR (KBr): 2984, 1716, 1599, 1500, 1390, 859 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, J = 7.2 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 5.21 (s, 2H), 7.06–7.16 (m, 4H), 7.22 (td, J = 1.5, 7.7 Hz, 1H), 7.29–7.34 (m, 2H), 8.04 (dd, J = 1.5, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.1, 61.1, 61.9, 115.1 (d, J = 21.75 Hz), 116.6, 117.5, 120.7, 122.9, 125.9, 126.2 (d, J = 3.4 Hz), 127.8, 131.5 (d, J = 8.3 Hz), 132.2, 141.6, 146.4, 162.0, 162.4 (d, J = 246 Hz); ESI-MS: m/z 360.99 $[M+Na]^+$; HRMS (EI, 70 eV) calcd for $C_{19}H_{15}FN_2O_3$ $[M^+]$ 338.1067, found 338.1053.

2-Carbethoxy-3-(2-methyl-4-nitrophenyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3j). Yield: 64%; solid, m.p.: 192–194 °C; IR (KBr): 2990, 1720, 1605, 1514, 1343, 1227, 1181, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 1.23 (t, J = 7.2 Hz, 3H), 2.29 (s, 3H), 4.28–4.31 (m, 2H), 5.05 (d, J = 13.8 Hz, 1H), 5.13 (d, J = 14.4 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.16 (td, J = 1.2, 7.8 Hz, 1H), 7.25 (td, J = 1.2, 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1 H), 8.06 (dd, J = 1.2, 7.8 Hz, 1H), 8.09 (dd, J = 2.4, 8.4 Hz, 1H), 8.18 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 13.9, 20.2, 61.3, 61.8, 116.6, 117.6, 118.6, 120.6, 123.1, 124.6, 125.8, 128.1, 131.1, 132.4, 137.4, 139.5, 142.1, 146.3, 147.7, 161.5; ESI-MS: m/z 402.03 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.28; H, 4.48; N, 11.14.

2-Carbethoxy-3-(4-carbomethoxyphenyl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (3k). Yield: 61%; solid, m.p.: 150–152 °C; IR (KBr): 2990, 1720, 1612, 1494, 1365, 1284, 1170, 863 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (t, J = 7.1 Hz, 3H), 3.95 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 5.24 (s, 2H), 7.07–7.16 (m, 2H), 7.21 (dd, J = 1.4, 7.7 Hz, 1H), 7.41 (d, J = 8.1 Hz, 2H), 8.05 (dd, J = 1.4, 7.9 Hz, 1H), 8.09 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.0, 52.1, 61.2, 61.9, 116.7, 117.5, 120.6, 122.9, 125.8, 127.9, 129.3, 129.8, 132.4, 135.2, 141.7, 146.4, 161.9, 166.7; ESI-MS: m/z 401.36 $[M+Na]^+$; HRMS (EI, 70 eV) calcd for $C_{21}H_{18}N_2O_5$ $[M^+]$ 378.1216, found 378.1216.

General procedure (condition B) for the synthesis of 3-aryl substituted pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones 4. To a well stirred and cooled (0–3 °C) solution of **9** (0.50 mmol) in 2 M hydrochloric acid (8.0 mL) was added a solution of $NaNO_2$ (48 mg, 0.70 mmol) in 2 mL H_2O dropwise during 45 min and the reaction mixture was allowed to stir for another 30 min at the same temperature. Ethyl 2-chloroacetoacetate (90 mg, 0.55 mmol) was added dropwise (during 2–3 min) at 0–3 °C. The temperature of the reaction mixture was then allowed to attain room temperature (rt) and stirred for another 5 h. It was then extracted with ethyl acetate (2 × 20 mL). The organic extracts were washed with water, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting crude product was refluxed (138–140 °C) in xylene (5.0 mL) in the presence of triethylamine (0.42 mL, 3.0 mmol) for few hours. Upon completion of the reaction (TLC), the solvent was removed *in vacuo* and extracted with ethyl acetate (2 × 20 mL).

Table 2 Synthesis of pyrazolo[1,5-*a*][1,4]benzodiazepin-6(4*H*)-ones **4** through intermediate **9**

Entry	Aryl Iodide (**6**) Ar	Products[a] **9** (Yield%)[b]	Products[c] **4** (Yield%)[d]	Heating time	Overall[e] (Yield%)
1	 **6a**	**9a** (85)	**4a** (43)	3.5 h	37
2	 **6b**	**9b** (87)	**4b** (57)	3.5 h	50
3	 **6m**	**9c** (71)	**4c** (45)	3.5 h	32
4	 **6e**	**9d** (82)	**4d** (48)	4.0 h	39
5	 **6g**	**9e** (72)	**4e** (41)	2.5 h	30
6	 **6n**	**9f** (72)	**4f** (42)	2.5 h	30
7	 **6i**	**9g** (74)	**4g** (37)	4.0 h	27
8	 **6j**	**9h** (80)	**4h** (38)	2.5 h	30

[a] Reaction conditions: iodide **6** (1.0 mmol.), acetylene **7b** (1.05 mmol), $Pd(PPh_3)_2Cl_2$ (0.04 mmol), CuI (0.06 mmol), Et_3N (7.0 mmol) in dry DMF (4 mL) stirred at rt for 2 h. [b] Chromatographically isolated pure products. [c] Reaction conditions: **9** (0.50 mmol), 2 M hydrochloric acid (5 mL), aqueous solution of $NaNO_2$ (1.4 equiv.), stirred at 0–3 °C for 30 min. Ethyl 2-chloroacetoacetate (0.55 mmol) was added followed by stirring at rt for 5 h. After usual work-up a crude product **11** was obtained and it was heated in xylene (5 mL) under reflux (140 °C) in the presence of Et_3N (6.0 equiv.). [d] Chromatographically isolated pure products and yields were calculated based on the alkyne **9**. [e] Overall yield was calculated based on starting iodide **6**.

The combined organic extracts were washed with water (15 mL), dried over Na_2SO_4, filtered and concentrated. The resulting crude product was purified through silica gel (100–200 mesh) column chromatography (40–50% ethyl acetate in petroleum ether, v/v) to furnish the desired product **4**.

2-Carbethoxy-5-methyl-3-phenyl-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (4a). Yield 43%; Solid, mp 134–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (t, J = 7.1 Hz, 3H), 3.15 (s, 3H), 4.26 (br, 2H), 4.32 (q, J = 7.1 Hz, 2H), 7.34–7.53 (m, 6H), 7.66 (td, J = 7.7, 1.1 Hz, 1H), 8.03 (t, J = 6.45 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 35.6, 42.3, 61.0, 122.9, 123.0, 127.5, 127.9, 128.0, 128.1, 130.0, 130.6, 131.7, 132.4, 135.3, 139.5, 142.3, 161.8, 166.7; IR (KBr, cm^{-1}) 2986, 2926, 1725, 1633, 1478, 1285, 1173; MS (ESI) (m/z) 384.19 (M+Na$^+$). Anal. Calcd for $C_{21}H_{19}N_3O_3$: C, 69.79; H, 5.30; N, 11.63; Found: C, 69.81; H, 5.33; N, 11.60.

2-Carbethoxy-5-methyl-3-(1-naphthyl)-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (4b). Yield 57%; Solid, mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, J = 7.1 Hz, 3H), 2.99 (s, 3H), 4.04–4.13 (m, 4H), 7.38–7.46 (m, 2H), 7.49–7.60 (m, 4H), 7.70 (td, J = 7.4, 1.5 Hz, 1H), 7.94 (t, J = 7.2 Hz, 2H), 8.04 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 35.7, 42.2, 60.6, 120.4, 122.8, 124.9, 125.4, 125.9, 126.2, 127.5, 127.9, 128.0, 128.1, 128.5, 128.6, 131.7, 132.3, 132.9, 133.3, 135.3, 140.5, 143.6, 161.4, 166.6; IR (KBr, cm^{-1}) 2981, 1725, 1643, 1480, 1168; MS (ESI) (m/z) 434.24 (M+Na$^+$). Anal. Calcd for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.14; N, 10.21. Found: C, 72.94; H, 5.12; N, 10.25.

2-Carbethoxy-5-methyl-3-(4-methylphenyl)-pyrazolo[l,5-*a*][1,4]-benzodiazepin-6(4*H*)-one (4d). Yield 48%; Solid, mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 3H), 2.42 (s, 3H), 3.15 (s, 3H), 4.25 (br, 2H), 4.33 (q, J = 7.1 Hz, 2H), 7.23–7.29 (m, 4H), 7.49 (t, J = 7.7 Hz, 1H), 7.66 (t, J = 7.7 Hz, 1H), 8.02 (t, J = 7.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 21.0, 35.4, 42.1, 60.8, 122.7, 122.8, 127.3, 127.7, 128.7, 129.7, 131.5, 132.2, 135.2, 137.5, 139.4, 142.1, 161.7, 166.5; IR (KBr, cm^{-1}) 2923, 1720, 1636, 1480, 1385, 1172; MS (ESI) (m/z) 398.07 (M+Na$^+$). HRMS (EI, 70 eV) calcd for $C_{22}H_{21}N_3O_3$ [M$^+$] 375.1583, found 375.1579.

2-Carbethoxy-5-methyl-3-(3-methoxyphenyl)-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (4f). Yield 42%; Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 3H), 3.16 (s, 3H), 3.85 (s, 3H), 4.27–4.36 (m, 4H), 6.90–6.98 (m, 3H), 7.38 (t, J = 7.8 Hz, 1H), 7.50 (td, J = 7.6, 1.1 Hz, 1H), 7.66 (td, J = 7.8, 1.5 Hz, 1H), 8.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 35.7, 42.3, 55.2, 61.0, 113.2, 116.1, 122.5, 122.8, 122.9, 127.5, 128.0, 129.2, 131.7, 132.0, 132.4, 135.4, 139.5, 142.3, 159.2, 161.8, 166.7; IR (KBr, cm^{-1}) 2932, 1723, 1643, 1479, 1289, 1232, 1169; MS (ESI) (m/z) 414.13 (M+Na$^+$). Anal. Calcd. for $C_{22}H_{21}N_3O_4$: C, 67.51; H, 5.41; N, 10.74. Found: C, 67.45; H, 5.44; N, 10.72.

2-Carbethoxy-5-methyl-3-[(2,4-dimethoxy)pyrimidine-5-yl]-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (4g). Yield 37%; Solid, mp 114–116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 3.16 (s, 3H), 3.97 (s, 3H), 4.07 (s, 3H), 4.22 (br, 2H), 4.33 (q, J = 7.1 Hz, 2H)), 7.51 (t, J = 7.5 Hz, 1H), 7.66 (t, J = 7.4 Hz, 1H), 8.02 (t, J = 9.0 Hz, 2H), 8.16 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 35.9, 42.5, 54.1, 54.9, 61.1, 105.8, 113.4, 122.9, 127.4, 128.1, 131.7, 132.4, 135.2, 140.3, 143.2, 158.6, 161.5, 165.3, 166.6, 168.9; IR (KBr, cm^{-1})2986, 1721, 1646, 1561, 1475, 1387, 1181; MS (ESI) (m/z) 446.16 (M+Na$^+$). Anal. Calcd. for $C_{21}H_{21}N_5O_5$: C, 59.57; H, 5.00; N, 16.54. Found: C, 59.54; H, 5.04; N, 16.59.

Synthesis of 2-carbethoxy-5-methyl-3-(uracil-5-yl)-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (13)

To a well-stirred solution of **4g** (85 mg, 0.20 mmol) in acetonitrile (4.0 mL) was added anhydrous sodium iodide (90 mg, 0.60 mmol) followed by chlorotrimethylsilane (0.60 mmol, 65 mg) under an argon atmosphere. The reaction mixture was then allowed to stir at room temperature for 24 h. The solvent was evaporated under reduced pressure and the residue was washed with aqueous sodium metabisulfite solution (3 mL) and water (3 mL), successively. It was then filtered and dried to furnish the pure product **13**.

The same procedure was adopted for the conversion of compound **3i** to product **12**.

2-Carbethoxy-3-(uracil-5-yl)-4*H*-pyrazolo[5,1-*c*][1,4]benzoxazine (12). Yield: 84%; solid, m.p.: >300 °C; IR (KBr): 3260, 3199, 3076, 1736, 1696, 1505, 1312, 1209 cm^{-1}; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.25 (t, J = 7.1 Hz, 3H), 4.23 (q, J = 7.1 Hz, 2H), 5.31 (s, 2H), 7.15–7.30 (m, 3H), 7.61 (d, J = 6.0 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 11.16 (d, J = 5.1 Hz, 1H), 11.32 (s, 1H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 14.0, 60.5, 62.2, 102.6, 111.9,115.8, 117.7, 123.0, 125.5, 127.9, 133.5, 141.5, 142.7, 146.2, 151.2, 161.5, 162.9; ESI-MS: m/z 377.08 [M+Na]$^+$; HRMS (EI, 70 eV) calcd for $C_{17}H_{14}N_4O_5$ [M$^+$] 354.0964, found 354.0965.

2-Carbethoxy-5-methyl-3-(uracil-5-yl)-pyrazolo[l,5-*a*][1,4]benzodiazepin-6(4*H*)-one (13). Yield 73%; Solid, mp >300 °C; IR (KBr, cm^{-1}) 3154, 1718, 1675, 1632, 1482, 1427, 1225, 1191; ^{1}H NMR (600 MHz, DMSO-d_6) δ 1.23 (t, J = 7.2 Hz, 3H), 3.08 (s, 3H), 4.22 (q, J = 7.2 Hz, 2H)), 4.38 (s, 2H), 7.55–7.58 (m, 2H), 7.75 (td, J = 7.65, 1.5 Hz, 1H), 7.82 (d, J = 7.8 Hz, 1H), 7.90 (dd, J = 7.8, 1.2 Hz, 1H), 11.12 (dd, J = 5.7, 1.5 Hz, 1H), 11.31 (s, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 14.0, 35.3, 41.6, 60.4, 103.0, 113.5, 122.2, 127.6, 128.0, 131.6, 132.6, 134.8, 141.6, 141.7, 143.3, 151.3, 161.3, 163.4, 165.7; MS (ESI) (m/z) 418.15 (M+Na$^+$). Anal. Calcd. for $C_{19}H_{17}N_5O_5$: C, 57.72; H, 4.33; N, 17.71. Found: C, 57.76; H, 4.35; N, 17.65.

Acknowledgements

Partial financial support from CSIR network projects (IAP 0001 and NWP-0009) is gratefully acknowledged. K.B. and A.K.S are thankful to CSIR, New Delhi for their fellowships.

Notes and references

1 (*a*) M. J. Cline and C. M. Haskell, *Cancer Chemotherapy*, W. B. Saunders co.Philadelphia, 1975; (*b*) Y. Minami, K.-i. Yoshida, R. Azuma, M. Saeki and T. Otani, *Tetrahedron Lett.*, 1993, **34**, 2633; (*c*) T. Hirata, H. Saito, H. Tomioka, K. Sato, J. Jidoi, K. Hosoe and T. Hidaka, *Antimicrob. Agents Chemother.*, 1995, **39**, 2295; (*d*) M.-Z. Huang, F.-X. Luo, H.-B. Mo, Y.-G. Ren, X.-G. Wang, X.-M. Ou, M.-X. Lei, A. P. Liu, L. Huang and M. C. Xu, *J. Agric. Food Chem.*, 2009, **57**, 9585.

2 (*a*) P. J. Colemam, M. E. Fraley, R. M. Garbaccio and L. A. Neilson, *PCT Patent Appl.*, 2006, WO 2006023083; Chem. Abstr., 2006, 144, 274279y; (*b*) A. Tahri, L. Hu, D. L. N. G. Surleraux and P. T. B. P. Wigerinck, *PCT Patent Appl*., 2006, WO 2006108828; Chem. Abstr., 2006, 145, 438608d; (*c*) J. Bentley, M. Bergauer, B. Bertani, M. Biagetti, M. Borriello, S. M. Bromidge, M. Gianotti, E. Granci, C. P. Leslie, A. Pasquarello and V. Zucchelli, *PCT Patent Appl*., 2006, WO 2006024517; Chem. Abstr., 2006, 144, 254134u.

3 A. A. Patchet and R. P. Nargund, *Annu. Rep. Med. Chem.*, 2000, **35**, 289.

4 (*a*) T. Kaneko, H. Wong, T. W. Doyle, W. C. Rose and W. T. Bradner, *J. Med. Chem.*, 1985, **28**, 388; (*b*) J. B. Hester. Jr., A. D. Rudzik and B. V. Kamdar, *J. Med. Chem.*, 1971, **14**, 1078; (*c*) W. Zhang, J. P. Williams, Y. Lu, T. Nagashima and Q. Chu, *Tetrahedron Lett.*, 2007, **48**, 563; (*d*) A. A. Santilli and T. S. Osdene, *U. S. Patent.*, 1969, 3,457,258; *Chem. Abstr.*, 1969, **71**, 101898; (*e*) R. M. Keenan, J. F. Callahan, J. M. Samanen, W. E. Bondinell, R. R. Calvo, L. Chen, C. DeBrosse, D. S. Eggleston, R. C. Haltiwanger, S. M. Hwang, D. R. Jakas, T. W. Ku, W. H. Miller, K. A. Newlander, A. Nichols, M. F. Parker, L. S. Southhall, I. Uzinskas, J. A. Vasko-Moser, J. W. Venslavsky, A. S. Wong and W. F. Huffman, *J. Med. Chem.*, 1999, **42**, 545.

5 (*a*) G. Broggini, M. Orlandi, A. Turconi and C. Zoni, *Org. Prep. Proced. Int.*, 2003, **35**, 609; (*b*) W. Frostl and L. Maitre, *Pharmacopsych*, 1989, **22**, 54; (*c*) S. R. Donohue and R. F. Dannals, *Tetrahedron Lett.*, 2009, **50**, 7271.

6 (*a*) A. G. Katsifis, M. E. McPhee, F. Mattner and D. D. Ridley, *Aust. J. Chem.*, 1999, **52**, 1061; (*b*) D. K. Mohapatra, P. K. Maity, M. Shabab and M. I. Khan, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5241.

7 For reviews: (*a*) B. Achari, S. B. Mandal, P. K. Dutta and C. Chowdhury, *Synlett.*, 2004, 2449; (*b*) J. Ilas, P. S. Anderluh, M. S. Dolenc and D. Kikelj, *Tetrahedron*, 2005, **61**, 7325; for others: (*c*) S. Kuwabe, K. E. Torraca and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 12202; (*d*) G. Chaudhuri, C. Chowdhury and N. G. Kundu, *Synlett*, 1998, 1273; (*e*) M. Largeron and M.-B. Fleury, *Tetrahedron Lett.*, 1998, **39**, 8999; (*f*) J. F. Bower, P. Szeto and T. Gallagher, *Org. Lett.*, 2007, **9**, 3283.

8 (*a*) C. Bagolini, P. De Witt, L. Pacifici and M. T. Ramacci, *J. Med. Chem.*, 1978, **21**, 476; (*b*) F. Ammadi, S. Boukhris, A. Souizi and G. Coudert, *Tetrahedron Lett.*, 1999, **40**, 6517; (*c*) K. Hemming and C. Loukou, *Tetrahedron*, 2004, **60**, 3349; (*d*) S. Marcaccini, M. Miliciani and R. Pepino, *Tetrahedron Lett.*, 2005, **46**, 711; (*e*) W. Zhang, J. P. Williams, Y. Lu, T. Nagashima and Q. Chu, *Tetrahedron Lett.*, 2007, **48**, 563 and see also reference 4e.

9 (*a*) B. Willy and T. J. J. Muller, *Org. Lett.*, 2011, **13**, 2082; (*b*) G. Shan, P. Liu and Y. Rao, *Org. Lett.*, 2011, **13**, 1746; (*c*) J. J. Neumann, M. Suri and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 7790; (*d*) K. Mohanan, A. R. Martin, L. Toupet, M. Smietana and J.-J. Vasseur, *Angew. Chem., Int. Ed.*, 2010, **49**, 3196; (*e*) C. Spiteri, S. Keeling and J. E. Moses, *Org. Lett.*, 2010, **12**, 3368; (*f*) B. S. Gerstenberger, M. R. Rauckhorst and J. T. Starr, *Org. Lett.*, 2009, **11**, 2097; (*g*) Q. Lin, D. Meloni, Y. Pan, M. Xia, J. Rodgers, S. Shepard, M. Li, L. Galya, B. Metcalf, T.-Y. Yue, P. Liu and J. Zhou, *Org. Lett.*, 2009, **11**, 1999; (*h*) R. Liu, Y. Zhu, L. Qin and S. Ji, *Synth. Commun.*, 2008, **38**, 249; (*i*) K. Makino, H. S. Kim and Y. Kurasawa, *J. Heterocycl. Chem.*, 1998, **35**, 489 and other references cited therein.

10 (*a*) L. Garanti and G. Zecchi, *Synthesis*, 1974, 815; (*b*) L. Garanti, A. Sala and G. Zecchi, *J. Org. Chem.*, 1977, **42**, 1389; (*c*) R. Fusco, L. Garanti and G. Zecchi, *Tetrahedron Lett.*, 1974, **15**, 269.

11 Using intramolecular nitrilimine cycloaddition, see: (*a*) L. Bruche and G. Zecchi, *Tetrahedron*, 1989, **45**, 7432. For others see: (*b*) F. Melani, L. Cecchi and G. Filacchioni, *J. Heterocycl. Chem.*, 1984, **21**, 813; (*c*) L. Cecchi and G. Filacchioni, *J. Heterocycl. Chem.*, 1983, **20**, 871; (*d*) G. Dattolo, G. Cirrincione, A. M. Almerico, I. D'Asdia and E. Aiello, *J. Heterocycl. Chem.*, 1982, **19**, 1237.

12 B. Avila, D. M. Solano, M. J. Haddadin and M. J. Kurth, *Org. Lett.*, 2011, **13**, 1060.

13 (*a*) L. Basolo, E. M. Beccalli, E. Borsini, G. Broggini, M. Khansaa and M. Rigamonti, *Eur. J. Org. Chem.*, 2010, 1694; (*b*) G. Broggini, I. D. Marchi, M. Martinelli, G. Paladino, T. Pilati and A. Terraneo, *Synthesis*, 2005, 2246; (*c*) G. Broggini, L. Garanti, G. Molteni, T. Pilati, A. Ponti and G. Zecchi, *Tetrahedron: Asymmetry*, 1999, **10**, 2203; (*d*) G. Broggini, G. Casalone, L. Garanti, G. Molteni, T. Pilati and G. Zecchi, *Tetrahedron: Asymmetry*, 1999, **10**, 4447.

14 (*a*) C. Chowdhury, S. B. Mandal and B. Achari, *Tetrahedron Lett.*, 2005, **46**, 8531; (*b*) C. Chowdhury, S. Mukherjee, B. Das and B. Achari, *J. Org. Chem.*, 2009, **74**, 3612; (*c*) C. Chowdhury, A. K. Sasmal and P. K. Dutta, *Tetrahedron Lett.*, 2009, **50**, 2678; (*d*) C. Chowdhury, A. K. Sasmal and B. Achari, *Org. Biomol. Chem.*, 2010, **8**, 4971; (*e*) C. Chowdhury, S. Mukherjee, B. Chakraborty and B. Achari, *Org. Biomol. Chem.*, 2011, **9**, 5856.

15 For review article, see: (*a*) A. S. Shawali, *Chem. Rev.*, 1993, **93**, 2731. For others, see: (*b*) R. Benelbaghdadi, A. Hasnaoui, J.-P. Lavergne, M. Giorgi and M. Pierrot, *Synth. Commun.*, 1998, **28**, 4221; (*c*) G. Molteni, G. Broggini and T. Pilati, *Tetrahedron: Asymmetry*, 2002, **13**, 2491; (*d*) G. Molteni, *Heterocycles*, 2005, **65**, 2513; (*e*) A. Lauria, A. Guarcello, G. Macaluso, G. Dattolo and A. M. Almerico, *Tetrahedron Lett.*, 2009, **50**, 7333.

16 (*a*) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; (*b*) K. Sonogashira, in*Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon, Oxford, 1991, vol 3, p.521.

17 R. R. Phillips, *Org. React.*, 1959, **10**, 143.

18 Product **3j** was crystallised by slow evaporation of a solution of dichloromethane–petroleum ether (1 : 1, v/v) at room temperature; crystal data: $C_{20}H_{17}N_3O_5$, M = 379.37, triclinic, space group $P\bar{1}$, a = 9.3525(4) Å, b = 10.0265(5) Å, c = 10.8420(5) Å, V = 907.85(7) Å^3, Z = 2, D_{calcd} = 1.388 Mg m^{-3}, T = 296(2)K, μ = 0.102 mm^{-1}, $F(000)$ = 396, λ = 0.71073 Å, processed reflections 13611 and unique reflections 3186, Final R factor = 0.0477. The crystal data has been deposited at Cambridge Crystallographic Data Centre [CCDC No. 838046]. Copies of the data can be obtained free of charge *via* www.ccdc.ac.uk/conts/retrieving.html or CCDC, 12 union Road, Cambridge CB2 1EZ, UK.

19 (*a*) C. Heidelberger, *Pyrimidine and Pyrimidine Antimetabolites in Cancer Medicines*, J. F. Holland and E. Frei, ed.; Lea and Febiger, Philadelphia, 1984, pp. 801–824; (*b*) T. Onishi, C. Mukai, R. Nakagawa, T. Sekiyama, M. Aoki, K. Suzuki, H. Nakazawa, N. Ono, Y. Ohmura, S. Iwayama, M. Okunishi and T. Tsuji, *J. Med. Chem.*, 2000, **43**, 278 and other references cited therein.

20 (*a*) B. Das, C. Chowdhury, D. Kumar, R. Sen, R. Roy, P. Das and M. Chatterjee, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6947; (*b*) V. Srivastava, M. P. Darokar, A. Fatima, J. K. Kumar, C. Chowdhury, H. O. Saxena, G. R. Dwivedi, K. Shrivastava, V. Gupta, S. K. Chattopadhyay, S. Luqman, M. M. Gupta, A. S. Negi and S. P. S. Khanuja, *Bioorg. Med. Chem.*, 2007, **15**, 518.

21 Cytotoxicity assays of compounds **12** and **13** against various cancer cell lines are currently under study.