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Rapid analogue synthesis of trisubstituted triazolo[4,3-*b*]pyridazines

Ian Collins,* José L. Castro and Leslie J. Street

Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, CM20 2QR, UK

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Abstract

A rapid analogue synthesis of biologically active 3,6,7-trisubstituted 1,2,4-triazolo[4,3-*b*]pyridazines was devised to give easy and selective variation of the three substituents through combinations of silicon-directed anion formation, palladium-catalysed couplings and S_NAr displacements.

Keywords: pyridazines; triazoles; coupling reactions; silicon; silicon compounds.

Trisubstituted 1,2,4-triazolo[4,3-*b*]pyridazines **1** (Fig. 1) have been identified as subtype selective ligands for the benzodiazepine binding site of GABA-A receptors and as such may provide anxiolytic drugs with improved side-effect profiles.[1,2] As part of our medicinal chemistry program in this area, we sought an efficient and general synthesis of **1** that would permit easy variation of the pendant groups. We saw the 6,7-dihalo-1,2,4-triazolo[4,3-*b*]pyridazine **2** as a desirable intermediate, anticipating discrimination between the chloroimidate and 7-halo substituent in the final stages of the synthesis by alkoxide displacements and palladium-catalysed couplings, respectively. Initial attempts to prepare **2** by halogenation of 7-unsubstituted 6-chloro- or 6-hydroxytriazolopyridazines were unsuccessful, as were metalations of related 6-alkoxytriazolopyridazines, and this led us to consider instead the early introduction of the 7-halo substituent in a masked form. The well precedented conversion of trialkylsilylarenes to aryl halides[3] suggested the trimethylsilylpyridazine **3**[4] as a suitable starting material. Although the electrophile-induced *ipso* desilylation of such electron deficient heteroarylsilanes is not established, the corresponding reaction of trialkylstannylpyridazines has been described.[5]

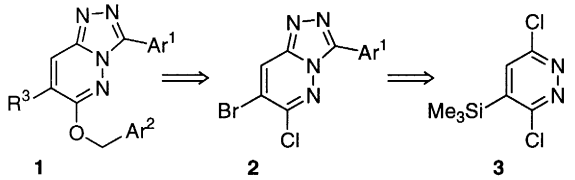

Fig. 1.

* Corresponding author. Fax: +44 1279 440187; e-mail: ian_collins@merck.com (I. Collins)

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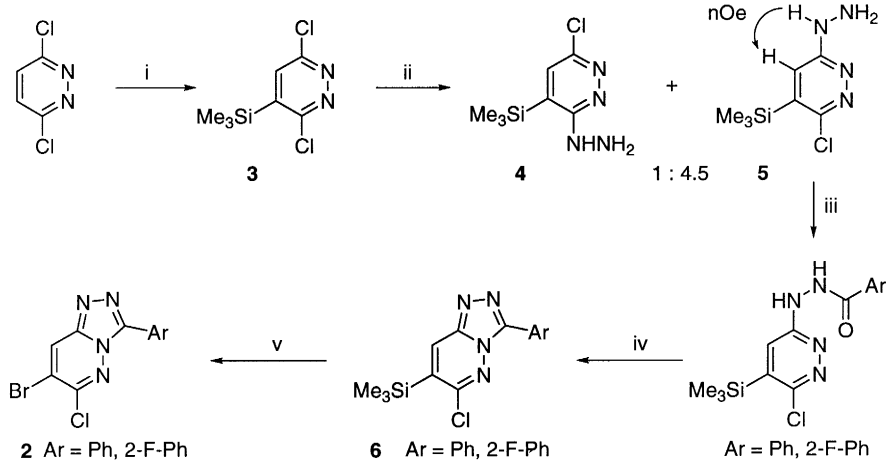
Compound **3** was prepared on a large scale by in situ quenching of the 4-lithio-anion of 3,6-dichloropyridazine[4,6] (Scheme 1). Direct conversion of **3** to the triazolopyridazine **6** was possible in poor yield (6%) under the standard harsh conditions[7] (benzoic hydrazide, $Et_3N{\cdot}HCl$, xylene, 140°C) accompanied by copious desilylation. A milder approach began with monodisplacement of chloride from **3** with anhydrous hydrazine to give quantitatively the separable hydrazinopyridazines **4** and **5**. The regiochemistry of the expected major product **5** was confirmed by the observed NOE. The use of a dry THF solution of hydrazine† was critical since hydrazine hydrate led to extensive desilylation. Acylation of **5** with aroyl chlorides was clean and high yielding when carried out in Et_2O, whereas in CH_2Cl_2 substantial diacylation occurred. The cyclisation of the hydrazide to the triazolopyridazine was accomplished by several means; treatment with $Et_3N{\cdot}HCl$ at 40°C yielded 48% of **6**, but competitive desilylation was again observed. Mitsunobu conditions (DEAD, PPh_3, Et_3N) gave a low yield (26%) of the product. Optimum conditions were found with triphenylphosphonium dibromide, generated in situ from triphenylphosphine and 1,2-dibromotetrachloroethane,[9] which gave **6** reliably in excellent yield.



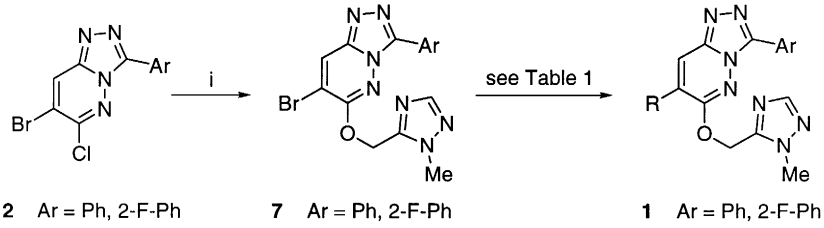
Scheme 1. Reagents and conditions: (i) LiTMP, TMSCl, THF, −78°C (67%); (ii) anhydrous NH_2NH_2, EtN^iPr_2, THF, reflux (99%); (iii) ArCOCl, Et_3N, Et_2O, 0°C (59–96%); (iv) $(BrCl_2C)_2$, PPh_3, Et_3N, MeCN, 0°C (91–97%); (v) $(BrF_2C)_2$, $[Bu_4N]^+[Ph_3SnF_2]^-$, THF, rt (88–98%)

The 7-trimethylsilyltriazolopyridazine **6** proved unreactive towards electrophilic *ipso* halogenation[3] (Br_2, ICl), reflecting the strongly electron-deficient nature of the heteroarene. Treatment with alkoxides displaced the 6-chloro substituent, but was accompanied by protodesilylation. This was reasoned to occur through generation of an anion equivalent at C-7, presumably a hypervalent silicon complex,[10] and this mode of reactivity was exploited to introduce the desired 7-bromo substituent. Thus the anion formed on desilylation with fluoride ion was captured by a soft electrophilic source of bromine to give the key dihaloheteroaromatic **2** in excellent yield.[11] Tetrabutylammonium triphenyldifluorostannate[12] provided a convenient, non-hygroscopic source of fluoride ion for this purpose. Multigram quantities of **2** were readily prepared by this route. To the best of our knowledge, this is the first time such a conversion of a heteroarylsilane to a heteroaryl bromide has been described.

Selective reaction of the chloroimidate group in **2** was achieved on treatment at low temperature with alkoxides, such as (2-methyl-2*H*-[1,2,4]triazol-3-yl)methanol[1] (Scheme 2). The resulting 7-bromo-6-alkoxytriazolopyridazines **7** underwent a variety of palladium-catalysed C–C bond forming reactions to complete the synthesis of the desired trisubstituted targets **1** (Table 1). For example, Stille,[13] Sonogashira,[14] Suzuki[15] and Negishi–Knochel[16,17] couplings were all successful. Although the condi-

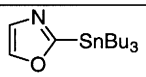
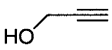
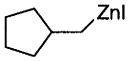
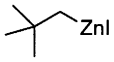
† CAUTION: Anhydrous solutions of hydrazine should not be over-concentrated as the neat reagent presents an explosion hazard.[8]

tions were not optimised, improvements in yields and in the reactivity of the heterocyclic bromide were seen with more active catalyst combinations (entries 3–5).[18] Thus a short and efficient route to the targets **1** was developed with the flexibility to vary the three substituents at will, two of these in the last two steps, which was of ready applicability to rapid analogue parallel synthesis.‡



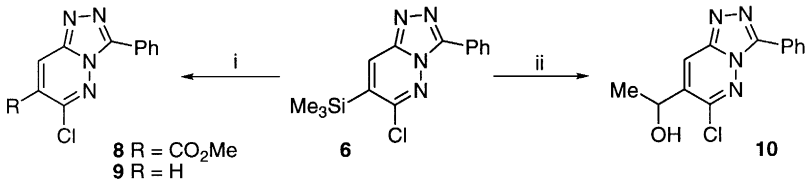
Scheme 2. Reagents and conditions: (i) (2-methyl-2*H*-[1,2,4]triazol-3-yl)methanol,[1] KHMDS, THF, 0°C (52–69%)

Table 1
Representative palladium-catalysed couplings to the bromides **7**

No.	Ar	R-M	Catalyst	Conditions	Yield (%)[a]
1[b]	Ph		$Pd(PPh_3)_4$	THF, 100°C, sealed tube	37[c]
2	Ph		CuI, $Pd(PPh_3)_4$	Et_3N, 90°C sealed tube	26
3[d]	Ph		Pd_2dba_3, $(2\text{-furyl})_3P$	DMF, 60°C	46
4[d]	2-F-Ph		Pd_2dba_3, $(2\text{-furyl})_3P$	DMF, 50°C	58
5	2-F-Ph	$PhB(OH)_2$	Pd_2dba_3, Ph_3As	DMF, 100°C	51

[a] Unoptimised isolated yields of purified material. [b] Organostannane prepared as described in ref. 20. [c] Also 23% recovered **7**. [d] Organozinc prepared as in ref. 17.

The use of the trimethylsilyl group as a masked anion was developed further to extend the diversity of substituents at the 7-position (Scheme 3). Treatment of **6** with stoichiometric fluoride ion in the presence of methyl cyanoformate gave the ester **8** and the desilylation–protonation product **9**. Alternatively, catalytic fluoride ion was sufficient to promote the reaction of **6** with aldehydes[6] to give the alcohols such as **10**. However, with less reactive or readily enolisable carbonyl compounds, e.g. cyclopentanone, only **9** was isolated. These compounds were elaborated as before to give further analogues of **1**.

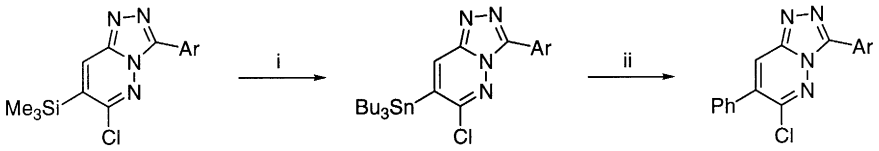


Scheme 3. Reagents and conditions: (i) $[(Me_2N)_3S]^+[Me_3SiF_2]^-$, MeO_2CCN, THF, rt (**8**, 21% and **9**, 25%); (ii) MeCHO, $[Bu_4N]^+[Ph_3SnF_2]^-$ (2×20 mol%), THF, rt (**10**, 75% and **9**, 10%)

Finally, the use of the heterocycle as the nucleophilic component in the palladium-catalysed coupling reactions was investigated. Transmetalation of the 7-trimethylsilyl group of **6** to the trialkylstannane **11** was achieved using Buchwald's conditions[19] (Scheme 4). The stannane **11** was indeed a competent

‡ All new compounds gave satisfactory ^1H NMR and MS data. In addition, compounds in Table 1 and compound **7** (Ar=Ph) gave satisfactory elemental analyses (C,H,N) and/or had purity of >97% as assessed by HPLC.

coupling partner in the Stille reaction with iodobenzene, but this reaction was markedly slower (2 days to completion) than the corresponding couplings of the heteroaryl bromides **7**. In the light of this, no further optimisation of this sequence was attempted.



6 Ar = 2-F-Ph **11** Ar = 2-F-Ph Ar = 2-F-Ph

Scheme 4. Reagents and conditions: (i) $(Bu_3Sn)_2O$, TBAF (3 mol%), THF, 60°C (18%); (ii) PhI, $Pd(PPh_3)_4$, DMF, 100°C (35%)

In summary, we have devised a short and flexible rapid analogue synthesis of trisubstituted triazolo[4,3-*b*]pyridazines of pharmacological interest that permits easy, selective variation of the three substituents by exploiting the potential of a heteroarylsilane to act as a masked anion. The biological activities of the compounds **1** and the application of this synthetic strategy to other heterocyclic systems will be reported in due course.

Acknowledgements

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