Pergamon

Tetrahedron Letters 40 (1999) 8419–8422

TETRAHEDRON LETTERS

2-(Alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines via Pd-mediated alkynylation of 2-chloro-4,6-dimethoxy-1,3,5-triazine

Rita Menicagli,* Simona Samaritani and Susanna Gori

Dipartimento di Chimica e Chimica Industriale and Centro di Studi del CNR per le Macromolecole Stereordinate ed Otticamente Attive, Via Risorgimento 35, 56126 Pisa, Italy

Received 29 July 1999; accepted 10 September 1999

Abstract

In the presence of a catalytic amount of $(Ph_3P)_4Pd$, 2-chloro-4,6-dimethoxy-1,3,5-triazine reacts with alk-1-ynes to give the corresponding 2-(alk-1′-ynyl)-derivatives in satisfactory yields. Depending on the nature of the alk-1-ynes, Pd(10%)/C can also be used to catalyze the cross-coupling. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: 2-chloro-4,6-dimethoxy-1,3,5-triazine; alk-1-ynes; palladium catalysts; coupling reaction.

Our recent studies[1–3] indicated that some 2,4,6-triheteroalkylsubstituted-1,3,5-triazines show appreciable antifungal activity against some common pathogenic fungi of both paper and plants. These results prompted us to investigate the biostatic activity of the less common 4,6-diheteroalkyl-1,3,5-triazines bearing a further C–C bonded substituent at the C_2 position.

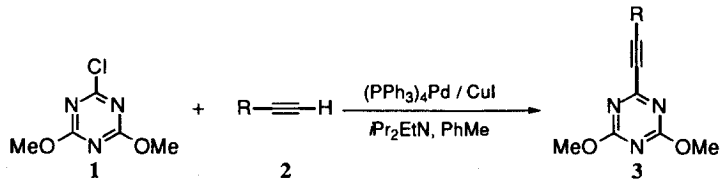
Taking into account the synthetic flexibility of the acetylenic function, the preparation of 2-(hex-1′-ynyl)-4,6-dimethoxy-1,3,5-triazine (**3a**) was first attempted via reaction of 2-chloro-4,6-dimethoxy-1,3,5-triazine (**1**) with a suitable acetylenic Grignard reagent. Since no trace of **3a** was detected in repeated experiments, carried out under different reaction conditions, the Sonogashira Pd-catalyzed cross-coupling[4] of **1** with hex-1-yne was attempted. While 2,4,6-tri(halo)-1,3,5-triazines are known to react both with trimethylsilylethynyllithium[5] and with tributylphenylethynyltin[6] in the presence of a catalytic amount of Pd(0) to give the corresponding symmetrically substituted derivatives, nothing is reported about the reactivity of 2-chloro-4,6-dialkoxy-1,3,5-triazines under the reaction conditions described by Sonogashira.[4] To the best of our knowledge, the only example of Pd(0)-mediated cross-couplings concerning haloalkoxy-1,3,5-triazines is the arylation of 2-alkoxy-4,6-dichloro-1,3,5-triazines via phenylboronic acid.[7]

In a preliminary experiment, the reaction between **1** and **2a** (Table 1, entry 1), performed in the presence of $(PPh_3)_4Pd$, CuI and Et_3N,[8] yielded the unexpected 2-*N*,*N*-diethylamino-4,6-dimethoxy-1,3,5-triazine as the main product.[9] Since the treatment of **1** with iPr_2EtN in PhMe at 80°C did not afford any trace of 2-alkylamino-4,6-dimethoxy-1,3,5-triazine, the following cross-coupling alkynylations were

* Corresponding author. Tel: +0039 50 918281; fax: +0039 50 918260; e-mail: rime@dcci.unipi.it

PII: S0040-4039(99)01737-2

Table 1
Synthesis of 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines (**3a–d**) by $(PPh_3)_4Pd/CuI/iPr_2EtN$ mediated cross-coupling of **1** and alk-1-ynes (**2a–d**)[a]



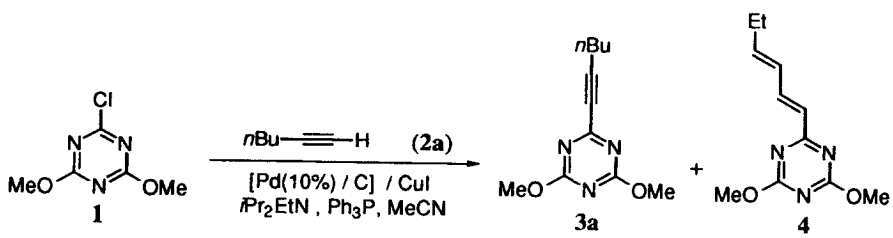
Entry	R	time (h)	**1** % conversion[b]	**3** % yield[c]
1[d]	*n*Bu- (**a**)	16[e]	100	20[f]
2	*n*Bu- (**a**)	29[e]	76	73
3	Ph- (**b**)	25[e]	96	69
4[g]	*t*Bu- (**c**)	96	50	46
5	MeEt(HO)C- (**d**)	72	100	90

[a] All reactions were carried out at 25°C, if not otherwise stated, by using a **1**/2/$(PPh_3)_4Pd/CuI/iPr_2EtN$ = 1/1.1/0.075/0.15/2.5 molar ratio; spectral data (I.R., ^1H, ^{13}C NMR, ms) and elemental analyses are in good agreement with the structure of the recovered chemically pure (Flash Chromatography) compounds.
[b] Glc evaluation.
[c] Determined on isolated compounds.
[d] Reaction carried out in the presence of Et_3N.
[e] The maximum conversion was reached after heating (55°C) the mixture for 72 h.
[f] The main component (80% yield) was 2-*N*,*N*-diethylamino-4,6-dimethoxy-1,3,5-triazine.
[g] An excess (2 equivalents) of **2c** was used.

carried out in the presence of this amine (Table 1, entries 2–5), adopting the same experimental procedure previously described.[8] The data reported in Table 1 shows that the Pd-catalyzed cross-coupling affords the corresponding systems **3a,b,d** in good yields; when 3,3-dimethylbut-1-yne (**2c**) was used, although an excess (2 equivalents, Table 1, entry 4) of this reagent was employed, the overall yield of **3c** was only 46%, owing to the low (50%) conversion reached.

Taking into account that Pd(10%)/C can also be successfully used to alkynylate aryl- and heteroarylhalides,[10] the reaction between **1** and **2a** was repeated in the presence of Pd(10%)/C Engelhard™ under the experimental conditions described by Guzmán et al.[10]

After 24 h the conversion of **1** was complete and, in the reaction mixture, along with **3a**, an appreciable amount of **4**[11] (Scheme 1, **3a**:**4** (3:1)) was also present. This unexpected result prompted us to repeat the reaction in the presence of a sample of Pd(10%)/C Aldrich™, since we had already found that the industrial source of the catalyst could affect the reaction pathway.[12] This experience allowed us to verify the lesser selectivity of Pd(10%)/C Aldrich™, giving a 1:1 mixture of **3a** and **4**. It was also found that the amount of iPr_2EtN affects the **3a**:**4** ratio. As a matter of fact, when Pd(10%)/C Engelhard™ and a iPr_2EtN:**1** (2.5:1) molar ratio instead of the reported[10] 18:1 were used, the yield of **3a** rose appreciably (**3a**:**4** (6:1)).



Scheme 1.

Table 2
Reactions of **1** with alk-1-ynes (**2b–e**) in the presence of the catalytic system [Pd(10%)/C]/CuI/PPh_3/iPr_2EtN[a]

Entry	R	time (h)	**1** % conversion[b]	**3** % yield[c]
1	Ph- (**b**)	70	100	100[b]
2[d]	*t*Bu- (**c**)	70	0	-
3	MeEt(HO)C- (**d**)	144	91	25[e]
4	*c*Hexyl- (**e**)	86	85	75

a) All reactions were carried out in MeCN at 55-65°C, if not otherwise stated, by using Pd(10%)/C Engelhard™ and a 1/2/[Pd(10%)/C]/CuI/PPh_3/iPr_2EtN = 1/1.1/0.04/0.04/0.16/2.5 molar ratio; spectral data (I.R., ^1H, ^{13}C NMR, ms) and elemental analyses agree well with the structure of the recovered chemically pure compounds.
b) Glc evaluation.
c) Determined on isolated compounds.
d) See Table 1, note g); reaction carried out at the boiling point (36-37°C) of **2c**.
e) In the reaction mixture appreciable amounts of unidentified by-products were observed.

On the basis of these preliminary findings, the following coupling reactions (Table 2) were performed using these last reaction conditions.

In all cases reported in Table 2, no trace of products were observed when the cross-coupling was carried out at 25°C for long reaction times, probably because under these experimental conditions formation of the catalytic active species (in situ) is prevented.

While the reaction between **1** and **2b** (Table 2, entry 1) proceeded comparably to the one described in Table 1 (entry 3), no trace of **3c** was obtained when Pd(10%)/C was used (Table 2, entry 2); although, taking into account the result obtained by using the more efficient $(PPh_3)_4Pd$ (Table 1, entry 4), a low yield of **3c** was expected, the failure of this experiment could be reasonably ascribed to the low boiling point of **2c**, which did not allow the reaction to be performed under suitable experimental conditions (Table 2). The prolonged reaction time necessary to obtain a good conversion of **2d** (Table 2, entry 3) caused the formation of appreciable amounts of unidentified by-products, thus reducing the yield of **3d** to 25%. It is nevertheless noteworthy that no trace of isomerization product was observed when **2e** was used in the coupling reaction (Table 2, entry 4).

In summary, the Pd(0) mediated cross-coupling between **1** and the reported alk-1-ynes provides a useful approach to the synthesis of 2-(alk-1′-ynyl)-4,6-dimethoxy-1,3,5-triazines (**3a–e**) and, reasonably, to the preparation of more complex 2-(alk-1′-ynyl)-4,6-dialkoxy-1,3,5-triazines. Studies are in progress to establish the antifungal activity of compounds **3a–e**.

Acknowledgements

This work was supported, in part, by the Ministero della Ricerca Scientifica e Tecnologica (MURST, Rome) and by C.N.R. (Comitato Nazionale Scienza e Tecnologia Beni Culturali).

References

1. Fanelli, C.; Fabbri, A. A.; Monti, S.; Menicagli, R.; Pini, D.; Rapaccini, S. M.; Samaritani, S.; Salvadori, P., 7th International Congress of Plant Pathology, Edinburgh (Scotland), 1998.
2. Samaritani, S.; Fabbri, A. A.; Fanelli, C.; Menicagli, R.; Salvadori, P., XXV Convegno Nazionale della Divisione di Chimica Organica, Folgaria (Italy), 1998.
3. Ricelli, A.; Fabbri, A. A.; Fanelli, C.; Menicagli, R.; Samaritani, S.; Pini, D.; Rapaccini, S. M.; Salvadori, P. *Restaurator* **1999**, 97–107.
4. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467–4470.

5. Kouvetakis, J.; Grotjahn, D.; Becker, P.; Moore, S.; Dupon, R. *Chem. Mater.* **1994**, *6*, 636–639.
6. Faust, R.; Göbelt, B. *Tetrahedron Lett.* **1997**, *38*, 8017–8020.
7. Janietz, D.; Bauer, M. *Synthesis* **1993**, 33–34.
8. Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. *Tetrahedron* **1998**, *54*, 135–156.
9. A chemically pure sample of 2-*N*,*N*-diethylamino-4,6-dimethoxy-1,3,5-triazine showed: ^{1}H NMR ($CDCl_3$): 3.85 (s, 6H), 3.52 (q, J=7.0 Hz, 4H), 1.1 (t, J=7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$): 171.9, 166.1, 54.0, 41.5, 12.8; m/e (I%): 212 (M^+, 32.6), 197 (35.9), 183 (100), 169 (49.7), 83 (34.9), 72 (63.2), 69 (29.7). Elemental analysis: calcd for $C_9H_{16}N_4O_2$: C, 50.93; H, 7.60; N, 26.40; O, 15.08. Found: C, 50.89; H, 7.62; N, 26.44; O, 15.04.
10. De la Rosa, M. A.; Velarde, E.; Guzman, A. *Synth. Commun.* **1990**, *20*, 2059–2064.
11. A chemically pure sample of **4** showed: ^{1}H NMR (C_6D_6): 7.97 (dd, J=15.3, J'=11.1 Hz, 1H), 6.54 (d, J=15.2 Hz, 1H), 6.06 (ddtd, J=15.2, J'=11.0, J''=1.3, J'''=0.6 Hz, 1H), 5.80 (dt, J=15.2, J'=6.6 Hz, 1H), 3.64 (s, 6H), 1.83 (dq, J=J'=7.5 Hz, 2H), 0.78 (t, J=7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$): 175.1, 172.4, 145.6, 143.3, 128.3, 126.5, 54.9, 26.1, 12.9; m/e (I%): 221 (M^+, 9.7), 206 (14.9), 192 (99.0), 135 (100), 120 (14.6), 106 (33.5), 101 (13.3), 92 (23.5), 78 (46.6), 72 (37.0), 69 (22.3), 65 (23.6), 58 (27.6). Elemental analysis: calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99; O, 14.46. Found: C, 59.74; H, 6.86; N, 18.96; O, 14.44.
12. Menicagli, R.; Wis, M. L.; Lardicci, L.; Botteghi, C.; Caccia, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 847–850.