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Tetrahedron Letters 47 (2006) 1649–1651
Tetrahedron Letters

A short synthesis of 3,3-di(hetero)arylpropylamines obtained from bis-(hetero)aryl ketones via palladium catalysis

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Received 1 December 2005; accepted 20 December 2005
Available online 19 January 2006

Abstract—A palladium-catalyzed parallel synthesis of bis-hetero(aryl) ketones is described with two further synthetic steps allowing easy entry to 3,3-di(hetero)arylpropylamines.
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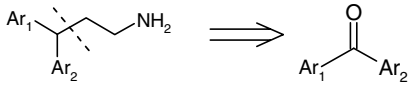
3,3-Diarylpropylamines are useful intermediates in the synthesis of biologically active compounds,[1] and display important biological properties in their own right.[2]

We were interested in synthesizing a number of 3,3-diarylpropylamines in which the aromatic rings either contained fluorine substituents, were heterocyclic, or possessed a combination of both.

We envisaged such amines to be derived from diaryl ketones (Scheme 1), and sought a reliable method for synthesizing such ketones from readily available starting materials, which could be performed in parallel.

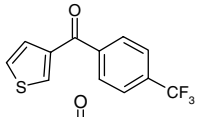
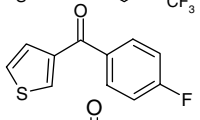
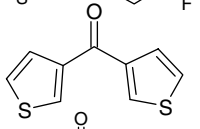
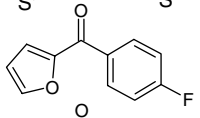
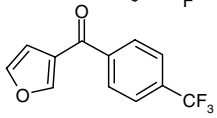
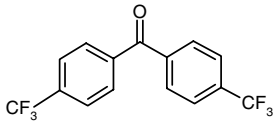
The efficient synthesis of ketones in general has been a target of research for many years. Since the reactivity of ketones is generally greater than that of their carboxylic acid precursors, this reactivity, or that of the reacting nucleophile must be suppressed in order to minimize multiple addition. Popular methods to achieve this include the use of Weinreb amides with Grignard reagents,[3] or the use of acid chlorides with organometallic reagents, notably zinc or cadmium compounds.[4]



Scheme 1.

Recently, palladium-catalyzed cross-coupling reactions have been described, which utilize thioesters or acid chlorides with boronic acids. These methods have proved very useful but in the case of thioesters, involve an extra synthetic step and stoichiometric amounts of

Table 1. Palladium-catalyzed ketone synthesis

No.	Product[a]	Yield (%)
1		44
2		46
3		48
4		80
5		53
6		38

[a] Aryl groups originating from boronic acids are drawn to the left of the carbonyl group.

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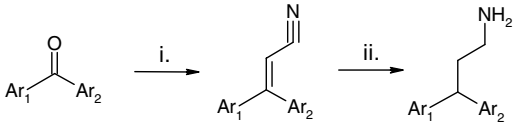
doi:10.1016/j.tetlet.2005.12.122

expensive reagents.[5] More recently, a palladium-catalyzed synthesis of aryl ketones has been described independently by Gooßen and Yamamoto, utilizing carboxylic and boronic acids as starting materials.[6] Requiring Palladium acetate as the source of Pd(0) and dimethylcarbonate to generate in situ the mixed anhydride for oxidative addition, we chose to carry out this method in a parallel synthesis array.[7] The results are summarized in Table 1.

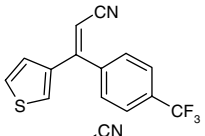
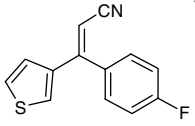
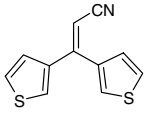
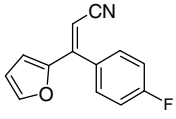
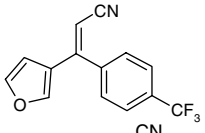
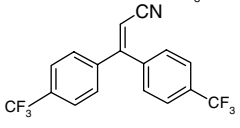
As can be seen in the table, yields are moderate to good, and we found the reaction to be very amenable to parallel synthesis. The conversion of ketones to 3,3-di(hetero)-arylpropylamines was achieved using a two-step procedure[8] involving Horner–Wadsworth–Emmons (HWE) olefination employing a cyanomethylphosphonate followed by hydrogenation (Scheme 2).

The HWE olefination proceeded smoothly to provide acrylonitriles in good yields. Hydrogenation was more problematic, however, and was found to be successful with substrates not containing a thiophene moiety (Table 2).[9]



Scheme 2. Conditions: (i) cyanomethylphosphonic acid ethyl ester, NaH, THF, 15 h, 0 °C to rt; (ii) H_2, Pd on carbon, methanol, rt.

Table 2. Synthesis and hydrogenation of acrylonitriles

No.	Acrylonitrile	Yield (%)[a]	Yield (%)[b]
7		83	—
8		76	—
9		76	—
10		86	36
11		65	40
12		40	57

[a] Yield of HWE olefination.
[b] Yield of hydrogenation.

In conclusion, we have shown that the synthesis of 3,3-di(hetero)arylpropylamines can be achieved by condensation of bis-(hetero)aryl ketones with an acetonitrile equivalent and that such ketones can be conveniently prepared in parallel via palladium catalysis. A limitation of this three-step method is the incompatibility of thiophenes in the transfer hydrogenation reaction, and current efforts are directed at overcoming this.

Acknowledgements

We gratefully acknowledge the services of the analytical chemistry department for NMR and mass spectral analyses.

References and notes

1. (a) Buschauer, A. *J. Med. Chem.* **1989**, *32*, 1963–1970; (b) Buschauer, A.; Friese-Kimmel, A.; Baumann, G.; Schunack, W. *Eur. J. Med. Chem. Chim. Ther.* **1992**, *27*, 321–330; (c) Ho, I.; James, G. *Tetrahedron* **1970**, *26*, 4277–4286.
2. (a) As antimuscarinic agents: Sparf, B.; Meese, C. Eur. Pat. Appl., 1999 (EP957073); (b) Johansson, R.; Moses, P.; Nilverbant, L.; Sparf, B. PCT Int. Appl., 1994 (WO9411337); (c) As calmodulin antagonists: Joensson, N.; Sparf, B.; Mikiver, L; Moses, P.; Nilvebrant, L.; Glas, G. Eur. Pat. Appl., 1989 (EP325571); (d) As cardiovascular agents: (i) Jpn. Kokai Tokkyo Koho, 1988 (JP63072657). (ii) Korbonits, D.; Szekeres, L.; Kovacs, G.; Santa, A.; Udvari, E.; Bata, I.; Marmarosi, K.; Tardos, L.; Kormoczy, P.; Gergely, V. Eur. Pat. Appl., 1988 (EP253327). (iii) Ibanez-Paniello, A. *An. Quim.* (1968–1979) **1975**, 810–814; (e) As CNS agents: (i) Pliai, K.; Prasad, C.; Kapil, R., *Ind. J. Chem., Sect. B* **1976**, *14B*, 714–716. (ii) Jones, G. US Patent US3446901, 1969.
3. (a) Ghosh, A. K.; Bilcer, G.; Schiltz, G. *Synthesis* **2001**, 2203; (b) List, B.; Castello, C. *Synlett* **2001**, 1687.
4. Irgolic, K. J. In *Houben-Weyl*; 4th ed. Klamann, D., Ed.; Thieme: Stuttgart, 1990; Vol. E12b, p 150.
5. (a) Liebeskind, L. S.; Srogl, J. *J. Am. Chem. Soc.* **2000**, *122*, 11260–11261; (b) Wittenberg, R.; Srogl, J.; Egi, M.; Liebeskind, L. S. *Org. Lett.* **2003**, *5*, 3033–3035.
6. (a) Gooßen, L. J.; Ghosh, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3458–3460; (b) Gooßen, L. J.; Ghosh, K. *Eur. J. Org. Chem.* **2002**, 3254–3267; (c) Gooßen, L. J.; Winkel, L.; Döhring, A.; Ghosh, K.; Pätzold, J. *Synlett* **2002**, *8*, 1237–1240; (d) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Chem. Lett.* **2001**, 1242–1243; (e) Kakino, R.; Yasumi, S.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 137–148; (f) Kakino, R.; Narahashi, H.; Shimizu, I.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1333–1345.
7. Typical procedure (as used for entry 4 in Table 1):
The reaction was carried out in parallel on a Mettler-Toldeo Miniblock-XT® parallel synthesizer. To a reaction vial was added 4-fluorobenzoic acid (2 g, 14 mmol), 2-furylboronic acid (1.9 g, 17 mmol), $Pd(OAc)_2$ (100 mg, 0.4 mmol) and tris(4-methoxyphenyl)phosphine (350 mg). A suspension containing dimethylcarbonate (3.8 g, 29 mmol), water (0.6 mL) and THF (25 mL) was added to this mixture, and the reaction vial flushed with Argon. The reaction mixture was stirred at 40 °C for 1 day. After this time, the contents were filtered through a plug of silica followed by flash chromatography (4:1 cyclohexane/ethyl acetate) to give the product of entry 4, Table 1 (2.2 g, 80%)

as a pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 6.79$–6.82 (1H, m), 7.38–7.44 (3H, m), 7.99–8.07 (2H, m), 8.12 (1H, s). LRMS: $m/z = 241$ [MH^+].

8. Typical procedure (as used for entry 10 in Table 2):
Step 1: To a stirred suspension of sodium hydride (930 mg, 60%, 23.3 mmol) in THF (10 mL) at 0 °C was added a solution of cyanomethylphosphonic acid ethyl ester (3.7 mL, 23.5 mmol) dropwise. The reaction was allowed to warm to rt and then a solution of ketone 10, Table 2 (2.2 g, 11.4 mmol) was added to this dropwise. After 15 h, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with NH_4Cl (aq) solution (10 mL) and water (10 mL). The organic phase was separated, dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (9:1 cyclohexane/ethyl acetate) provided the acrylonitrile as a yellow solid (mixture of cis and trans isomers). ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.81$ (1H, s, isomer a), 6.20 (1H, s, isomer b), 6.51 (1H, d, isomer b), 6.68 (1H, d, isomer b), 6.72 (1H, d, isomer a), 6.82 (1H, d, isomer a), 7.28–7.41 (4H, m, isomers a and b), 7.49–7.59 (4H, m, isomers a and b), 7.96 (1H, s, isomer b), 8.01 (1H, s, isomer a). LRMS: $m/z = 214$ [MH^+]. *Step 2*: The product from step 1 (1.2 g, 5.6 mmol) was dissolved in methanol (50 mL) and hydrogenated at rt under 3–4 bar pressure with Pd on carbon catalyst (0.5 g, 10%) and concd HCl (aq) (3 mL). After 15 h, the reaction was neutralized with NaOH (aq) and the organic layer separated and dried over $MgSO_4$. The solution was concentrated in vacuo and the crude solid purified by flash chromatography (9:1 DCM/MeOH) to give the amine (0.5 g, 36%) as a pale yellow solid. LRMS: $m/z = 220$ [MH^+].
9. Transfer hydrogenation utilizing Wilkinson's catalyst reported to be compatible with sulfur functional groups[10] was also unsuccessful.
10. For example: Donohoe, T. J. *Oxidation and Reductions in Organic Synthesis*; 2000, Oxford Science Publications.