Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 45 (2004) 1489–1493

Two-step synthesis of β-alkyl chalcones and their use in the synthesis of 3,5-diaryl-5-alkyl-4,5-dihydropyrazoles

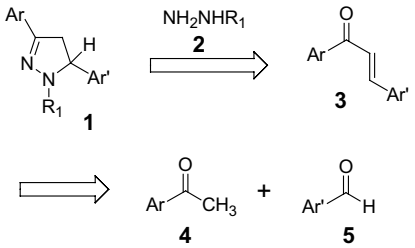
Christopher D. Cox,* Michael J. Breslin and Brenda J. Mariano

Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA

Received 17 November 2003; revised 3 December 2003; accepted 5 December 2003

Abstract—We report a simple and efficient two-step synthesis of variously substituted β-alkyl chalcones (**7**) from the corresponding Weinreb amide and a terminal alkyne, and that these chalcones are useful intermediates for the synthesis of medicinally interesting 3,5-diaryl-5-alkyl-4,5-dihydropyrazoles (**6**). The current methodology allows for the incorporation of many substitution patterns not available from the few previously reported approaches to compounds in this class.

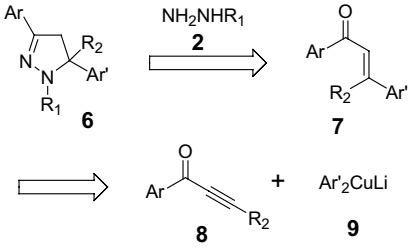
Heterocyclic rings have played an important role in medicinal chemistry, serving as key templates central to the development of numerous important therapeutic agents. Among the many five-membered heterocycles studied, 3,5-diaryl-4,5-dihydropyrazoles (**1**) have been identified as active core structures in anti-bacterial,[1] hypotensive,[2] and anti-inflammatory[3] agents, as well as in neurotoxicity inhibitors.[4] Synthetically, these molecules are readily accessible through the addition of a hydrazine to a chalcone (**3**), which in turn is easily prepared by either acid- or base-catalyzed condensation of an acetophenone with an aromatic aldehyde (Scheme 1). The fact that large combinatorial libraries have been based upon this methodology testifies to its robustness and wide applicability.[5]



Scheme 1. Retrosynthesis of 3,5-diaryl-4,5-dihydropyrazoles.

During the course of a medicinal chemistry effort, we became interested in accessing the corresponding 3,5-diaryl-5-alkyl analogs **6**, R_2 = alkyl. A search of the literature revealed that there is no general and convenient synthetic method to access these valuable structures;[6] however, addition of a hydrazine to a β-alkyl chalcone (**7**, R_2 = alkyl) could provide a direct and synthetically useful route to these targets (Scheme 2).[7]

Simple β-*methyl* chalcones with identical substitution patterns on both aromatic rings are readily available by self-condensation of an acetophenone.[8] On the other hand, non-symmetrical β-methyl chalcones, or chalcones with a different group at the β-position, prove more problematic synthetically.[9] Historically, complex β-alkyl chalcones have been made in various ways: (1) conjugate addition of a cuprate to a β-unsubstituted chalcone, trapping the resultant enolate with selenium, oxidation to the selenoxide, followed by elimination to the chalcone;[10] (2) conjugate addition of cyanide to a

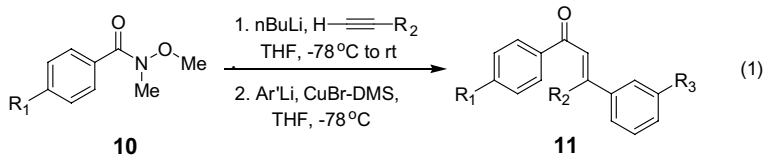


Scheme 2. Proposed retrosynthesis of 3,5-diaryl-5-alkyl-4,5-dihydropyrazoles.

Keywords: Alkyl chalcone; Dihydropyrazole; Cyclization; Aryl cuprate addition; Propargylic ketone.
* Corresponding author. Tel.: +1-215-652-2411; fax: +1-215-652-7310; e-mail: chris_cox@merck.com

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.026

Table 1. Preparation of β-alkyl chalcones[a]



(1)

Entry	R_1	R_2	R_3	Yield (%)
a	H	Me	H	91[b]
b	H	$(CH_2)_3OTBS$	H	74
c	H	CH_2OTHP	H	83
d	Br	$(CH_2)_2OTHP$	H	81
e	H	$(CH_2)_2Ph$	OTBS	56[c]

[a] Abbreviations: THP = tetrahydropyranyl; TBS = *tert*-butyldimethylsilyl; yields are reported for isolated, pure compounds. The products are mixtures of (*E*) and (*Z*) isomers; see text for discussion.
[b] This compound was made by the addition of 1-propynylmagnesium bromide to the Weinreb amide in the first step of the sequence.
[c] The low yield in this transformation reflects difficulty in isolation of the pure material.

β-unsubstituted chalcone, selective alkylation at the β-position, and elimination of cyanide;[9] (3) conjugate addition of an organozinc and copper reagent to a (2-propynylidene)morpholinium triflate, followed by hydrolysis;[11] and (4) palladium(0)-catalyzed coupling of β-tributylstannyl chalcones with benzyl or aryl halides.[12] These methods all suffer from limitations due to the handling of toxic compounds, limited substrate scope, and/or long synthetic routes, making such procedures cumbersome when a large number of derivatives are required for studying structure–activity relationships (SAR) against biological targets.

A conceptually attractive approach to β-alkyl chalcones is the addition of an arylcuprate to a propargylic ketone (Scheme 2).[13] Such a convenient and efficient route to these targets is a crucial first step for wide application of the proposed methodology to access structures **6** (R_2 = alkyl), and is also of value because chalcones themselves have interesting biological properties worthy of further study.[14] In this communication, we report a simple, two-step procedure for the synthesis of β-alkyl chalcones in good yield from a Weinreb amide and a terminal alkyne, and that these chalcones are useful intermediates for the synthesis of variously N1-substituted 3,5-diaryl-5-alkyl-4,5-dihydropyrazoles (**6**).

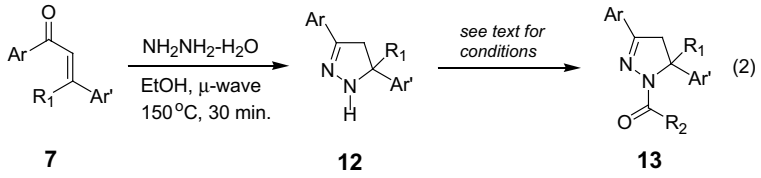
Our first task in this endeavor was to develop a short and efficient synthesis of the necessary β-alkyl chalcones. In doing so, we required that the methodology be amenable to various substitution patterns on both aryl rings, as well as allowing for the introduction of functionalized alkyl groups at the β-position (cf., not just simple alkyl). In this vein, we investigated the sequence pictured in Eq. 1. Weinreb amides, available commercially or readily prepared from the acid or acid chloride, react smoothly with the lithium anion of a terminal alkyne to provide the propargylic ketones. Reaction of these intermediates occurs at −78 °C with the cuprate derived from CuBr·DMS and commercially available phenyllithium, or an aryllithium obtained via halogen–metal exchange from a suitably functionalized aryl halide, to provide the desired β-alkyl chalcones in good overall yield.

Utilizing this methodology, the simple β-methyl chalcone **11a** is available in high yield, as are the β-functionalized derivatives in entries b and c of Table 1.[15] The protected alcohol moiety of various chain length present in these analogs serves as a convenient handle for the introduction of functionality in the side chain following cyclization to the dihydropyrazole nucleus (vide infra). As illustrated in entry d, halides can be easily incorporated in the western aryl portion, allowing for further diversity, if desired, via transition metal-mediated chemistry. Finally, functionalized eastern aryl rings can be incorporated, provided that the substituents are stable to the metalation conditions employed (entry e). It should be noted that chalcones **11** in Table 1 are formed as mixtures of double bond isomers in a ratio that varied between 1:1 and 2:1. Although these isomers were separable, they were not routinely isolated since both converge to the same product upon cyclization to the dihydropyrazole.

We next investigated the potential of β-alkyl chalcones in the synthesis of dihydropyrazoles. To this end, we found that hydrazine hydrate smoothly adds to these chalcones within 30 min in EtOH at 150 °C under microwave irradiation (Eq. 2).[16] Microwave heating is not a requirement for these reactions, as refluxing overnight in EtOH provided similar results; however, the shorter reaction times and the ability to easily perform multiple reactions in parallel with an automated handling system make the microwave route a more attractive option for the synthesis of moderately sized libraries.

Dihydropyrazoles such as **12** without substitution at N1 have been shown to rapidly undergo ene reaction with O_2,[17] and, not surprisingly, could not be purified by either normal or reverse phase chromatography. However, following concentration of the reaction mixture and dissolving the residue in CH_2Cl_2, **12** reacts effi-

Table 2. Synthesis of l-acyl-3,5-diaryl-5-alkyl-4,5-dihydropyrazoles[a]



7 **12** **13**

Entry	Ar	R_1[b]	Ar′	R_2	Yield (%)
a	Ph	Me	Ph	NHPh	86
b	Ph	Me	Ph	NHEt	75
c	Ph	$(CH_2)_2Ph$	3-HOPh	NMe_2	70
d	Ph	$(CH_2)_3OH$	Ph	NMe(cyclohexyl)	77
e	Ph	$(CH_2)_3OH$	Ph		76
f	4-BrPh	$(CH_2)_2OH$	Ph	NH_2	65
g	Ph	Me	Ph	$CH_2CH_2CH_3$	81
h	Ph	Me	Ph	Ph	79

[a] Yields are reported for isolated, pure compounds.

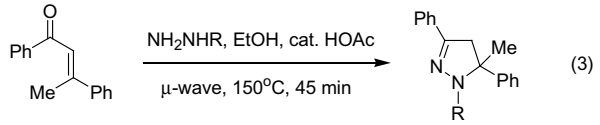
[b] R_1 substitution in the chalcones **7d**–**7f** is the protected from of the alcohol (**7d** and **7e**, as the *tert*-butyldimethylsilyl-alcohol; **7f**, as the tetrahydropyranyl-alcohol). The final products **13d** and **13e** were made by deprotection with triethylamine trihydrofluoride in CH_3CN; **13f** was made by stirring in THF/MeOH with a catalytic amount of Amberlyst 15 ion-exchange resin.

ciently with a number of electrophiles to form stable N1-acyl dihydropyrazoles as depicted in Table 2.

Addition of aryl or alkyl isocyanates to **12** provides the desired N1-urea dihydropyrazoles **13a** and **13b** in good yield. Surprisingly, attempts to reach *N*,*N*-dimethyl urea **13c** by acylation of **12** with dimethylcarbamoyl chloride were unsuccessful, resulting in no reaction. After some experimentation, we found that **12** reacts with triphosgene to form the putative carbamoyl chloride, which can be treated with symmetrical, non-symmetrical, and cyclic amines (entries c, d, and e), as well as ammonia (entry f) to provide dihydropyrazoles **13** in good yields.[18] In contrast to the case with carbamoyl chlorides, **12** does react with acyl chlorides such as butyryl chloride and benzoyl chloride to provide **13g** and **13h**, respectively. All attempts to sulfonylate **12** were unsuccessful. The alcohol functionality in the side chain of dihydropyrazoles **13d**–**f** can be converted to a number of other important functional groups such as aldehyde, acid, amine, and ether for additional diversity.[19]

To further explore the potential of β-alkyl chalcones in the synthesis of 3,5-diaryl-5-alkyl-4,5-dihydropyrazoles, we examined N1 alkyl and aryl substitution as illustrated in Eq. 3. By increasing the reaction time to 45 min and adding a catalytic amount of acetic acid, methylhydrazine, and ethyl hydrazinoacetate cyclize to form the desired heterocycles in satisfactory yields. Unfortunately, arylhydrazines perform poorly under these conditions. Analysis of the NMR spectrum of the crude reaction of **11a** with phenylhydrazine indicates that only a small amount of desired product was formed, as evidenced by the diagnostic AB quartet at δ 3.4 ppm attributable to the protons at C-4 of the dihydropyrazole ring. When the same reaction is performed with the more nucleophilic 4-methoxyphenylhydrazine, analysis of the crude NMR indicates much higher conversion (~50%); however, attempts to isolate the product were unsuccessful. We have noted some instability toward acidic conditions of 1-alkyl-3,5-diaryl-5-alkyl-4,5-dihydropyrazoles such as **14b**, and this may be related to our inability to isolate the corresponding N1-aryl dihydropyroles following silica gel chromatography.[20]

In conclusion, we have disclosed a simple, two-step procedure for the synthesis of diverse β-alkyl chalcones from the Weinreb amide and a terminal alkyne, and that these chalcones are useful intermediates for the synthesis of 3,5-diaryl-5-alkyl-4,5-dihydropyrazoles with various substitution patterns at N1. In a forthcoming paper, we will demonstrate how this versatile methodology allowed us to pursue a fruitful medicinal chemistry effort within this structural class.



11a

14a R = Me, 51%
14b R = CH_2CO_2Et, 70%
14c R = Ph, ~ 10% (not isolated)

Acknowledgements

We thank Dr. Charles Ross and Ms. Joan Murphy for performing the high resolution mass spectral analyses, and Dr. Steven M. Pitzenberger for 1D NOE analysis.

References and notes

1. (a) Sachchar, S. P.; Singh, A. K. *J. Indian Chem. Soc.* **1985**, *62*, 142–146; (b) Havaldar, F. H.; Fernandes, P. S. *J. Indian Chem. Soc.* **1988**, *65*, 691–694; (c) Cihat, C.; Tayhan, A.; Sarac, S.; Yuluğ, N. *J. Indian Chem. Soc.* **1990**, *67*, 571–574.
2. Turan-Zitouni, G.; Chevallet, P.; Kilic, F. S.; Erol, K. *Eur. J. Med. Chem.* **2000**, *35*, 635–641.
3. Satti, N. K.; Suri, K. A.; Suri, O. P. *Indian Drugs* **1987**, *24*, 492–493.
4. Shshikura, J.; Inami, H.; Kaku, H.; Yamahita, H.; Ohno, K.; Tsutsumi, R. PCT WO 01/32173 A1, **2001**.
5. (a) Powers, D. G.; Casebier, D. S.; Fokas, D.; Ryan, W. J.; Troth, J. R.; Coffen, D. L. *Tetrahedron* **1998**, *54*, 4085–4096; (b) Bauer, U.; Egner, B. J.; Nilsson, I.; Berghult, M. *Tetrahedron Lett.* **2000**, *41*, 2713–2717.
6. Although there are reports in the literature of compounds in this class, they are very limited in terms of the substitution patterns available by the reported methodology; see: (a) Harris, D. J.; Kan, G. Y.-P.; Tschamber, T.; Snieckus, V. *Can. J. Chem.* **1980**, *58*, 494–500; (b) Matsumura, N.; Kunugihara, A.; Yoneda, S. *Tetrahedron Lett.* **1984**, *25*, 4529–4532; (c) Molina, P.; Tárrage, A.; Serrano, C. *Tetrahedron* **1984**, *40*, 4901–4910; (d) Jain, R.; Sponsler, M. B.; Coms, F. D.; Dougherty, D. A. *J. Am. Chem. Soc.* **1988**, *110*, 1356–1366.
7. This addition has been reported; see: (a) El-Sharief, A. M.; Ammar, Y. A.; Mohamed, Y. A.; Zaki, M. E. A. *J. Indian Chem. Soc.* **1984**, *61*, 537–543; (b) Morkovnik, A. S.; Okhlobystin, O. *Chem. Heterocycl. Chem. (Engl. Transl.)* **1985**, *21*, 461–464.
8. Wayne, W.; Adkins, H. In *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. 3, pp 367–369.
9. Nielsen, S. F.; Kharazmi, A.; Christensen, S. B. *Bioorg. Med. Chem. Lett.* **1998**, *6*, 937–945, and references cited therein.
10. Pelter, A.; Ward, R. S.; Ohlendorf, D.; Ashdown, D. H. J. *Tetrahedron* **1979**, *35*, 531–533.
11. Brunner, M.; Maas, G. *Synthesis* **1995**, 957–963.
12. Takeda, T.; Kabasawa, Y.; Fujiwara, T. *Tetrahedron* **1995**, *51*, 2515–2524.
13. A search of the Beilstein CrossFire Database only identified several examples of the formation of a β-alkyl chalcone from a propargylic ketone. In all cases, it involved the addition of an alkyl nucleophile to a diaryl propargylic ketone: (a) Kohler, E. P.; Barrett, G. R. *J. Am. Chem. Soc.* **1924**, *46*, 747–753; (b) Fouli, F. A.; Basyouni, M. N. *Acta Chim. Acad. Sci. Hung.* **1981**, *106*, 297–302; (c) Ref. 11.
14. (a) Ref. 9; (b) Kidwai, M.; Misra, P. *Synth. Commun.* **1999**, *29*, 3237–3250; (c) Potter, G. A.; Butler, P. C.; Wanogho, E. PCT WO 2001/072680, **2001**.
15. General procedure for the synthesis of β-alkyl chalcones: 6-{[*tert*-butyl(dimethyl)silyl]oxy}-1,3-diphenylhex-2-en-1-one(**11b**). To a solution of 5.0 g (25.4 mmol) of *tert*-butyldimethyl-pent-4-ynyloxy-silane (Koseki, Y.; Sato, H.; Watanabe, Y.; Nagasaka, T. *Org. Lett*. **2002**, *4*, 885–888) in 100 mL of THF at −78 °C under an atmosphere of N_2 was added dropwise 10.2 mL (25.4 mmol) of 2.5 M *n*BuLi in hexane. After stirring for 1 h at that temperature, 4.0 g (24.2 mmol) of *N*-methoxy-*N*-methyl benzamide in 20 mL of THF was added, the cooling bath was removed, and stirring was continued for 3 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl, extracted with 2×EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The crude material was loaded onto a 40 g silica gel cartridge and eluted with a gradient of 0–55% EtOAc in hexanes over 25 min to provide 6.3 g (20.9 mmol, 87%) of the propargylic ketone as a pale yellow oil. To a suspension of 2.2 g (10.7 mmol) of CuBr·DMS in 30 mL of THF at −78 °C was added 10.7 mL (21.4 mmol) of a 2.0 M solution of PhLi in dibutylether. After stirring for 1.5 h, 2.7 g (8.9 mmol) of the above-prepared ketone in 5 mL of THF was added, and the mixture was allowed to stir for an additional 3 h at −78 °C, and warmed to 0 °C for 15 min before being quenched with saturated aqueous NH_4Cl. The mixture was partitioned with EtOAc, the layers were separated, the aqueous layer was extracted with 2×EtOAc, the organic layers were combined, washed with brine, dried over Na_2SO_4, and concentrated. The crude material was loaded onto a 40 g silica gel cartridge and eluted with a gradient of 0–25% EtOAc in hexanes to provide 2.89 g (7.6 mmol, 85%) of **11b** as a yellow oil; NMR analysis indicated that there was a 1.1:1 mixture of *E*:*Z* isomers. Careful separation of a fraction of this material provided the pure isomers, whose identities were determined by 1D NOE analysis. Data for **11b**-(***E***) (first to elute): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.0 (m, 2H), 7.6–7.4 (m, 8H), 7.1 (s, 1H), 3.7 (t, $J = 6.3$ Hz, 2H), 3.1 (m, 2H), 1.75 (m, 2H), 0.9 (s, 9H), 0.01 (s, 6H) ppm. Data for **11b**-(***Z***) (second to elute): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.8 (m, 2H) 7.45 (m, 1H), 7.35 (m, 2H), 7.25–7.1 (m, 5H), 6.7 (s, 1H), 3.65 (t, $J = 6.3$ Hz, 2H), 2.65 (t, $J = 7.6$ Hz, 2H), 1.7 (m, 2H), 0.9 (s, 9H), 0.05 (s, 6H) ppm. Data for **11b**: HRMS (ES) calcd M+H for $C_{24}H_{32}O_2Si$: 381.2245. Found: 381.2251.
16. This stands in contrast to the simple β-unsubstituted chalcones, which react completely within 5 min under these conditions, or in 1–2 h in refluxing CH_2Cl_2.
17. Baumstark, A. L.; Dotrong, M.; Vasquez, P. C. *Tetrahedron Lett.* **1987**, *28*, 1963–1966.
18. General procedure for cyclization/acylation of β-alkyl chalcones: 5-[2-(3-hydroxyphenyl)ethyl]-*N*,*N*-dimethyl-3,5-diphenyl-4,5-dihydro-1*H*-pyrazole-1-carboxamide (**13c**). To a solution of 282 mg (0.64 mmol) of **11e** in 3 mL of EtOH was added 62 μL (1.27 mmol) of hydrazine hydrate. The reaction was heated in the microwave for 30 min at 150 °C, cooled to room temperature, and concentrated by rotary evaporation. The residue was dissolved in 20 mL of THF, 180 μL (1.27 mmol) of triethylamine was added, followed by 94.5 mg (0.32 mmol) of triphosgene. After stirring for 7 h, 3.2 mL (6.4 mmol) of a 2 M solution of dimethylamine in THF was added, and stirring was continued overnight. The reaction was transferred to a separatory funnel with 10% aqueous citric acid and EtOAc, the layers were separated, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in 15 mL of anhydrous CH_3CN and 1.5 mL of triethylamine trihydrofluoride was added, and the mixture was stirred for 24 h. The reaction was then partitioned between saturated aqueous $NaHCO_3$ and EtOAc, the layers were separated, the organic layer was washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The residue was purified on a 12 g silica gel cartridge with a gradient of 10–100% EtOAc in hexanes over 15 min to provide 185 mg (0.45 mmol, 70%) of **13c** as a white solid. Data for **13c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (m, 2H), 7.4 (m, 3H), 7.3–7.1 (m, 6H), 7.05 (m, 1H), 6.75 (m, 1H), 6.7 (s, 1H), 6.45 (m, 1H), 3.35 (q, 2H), 3.25–3.15 (m, 1H), 3.1 (s, 6H), 2.7–2.6 (m, 1H), 2.5 (m, 1H), 2.3 (m, 1H) ppm. HRMS (APCI) calcd M+H for $C_{26}H_{27}N_3O_2$: 414.2176. Found: 414.2165.
19. In a series of closely related analogs, we found that the dihydropyrazole core is stable to oxidative (Dess–Martin Periodinane, cat. CrO_3/H_5IO_6), reductive [$LiBH_4$,

$Na(OAc)_3BH$] alkylative (NaH, DMF, RX), and nucleophilic (NaN_3, DMF, 80 °C) conditions.

20. A major product from the acid-promoted decomposition of N1-alkyl-3,5-diaryl-5-alkyl-4,5-dihydropyrazoles appears to be the product of a two electron oxidation, implicating the formation of the corresponding pyrrole; however, due to disubstitution at C5, this could only occur via rearrangement. A similar rearrangement has been noted in 1-sulfonyl-3,5-diaryl-5-alkyl-4,5-dihydropyrazoles under basic conditions; see: Lempert-Sreter, M.; Lempert, K. *Tetrahedron* **1975**, *31*, 1677–1682.