Selective N1-Alkylation of 3,4-Dihydropyrimidin-2(1*H*)-ones Using Mitsunobu-Type Conditions

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Abstract: The regioselective N1-alkylation of 3,4-dihydropyrimidin-2(1*H*)-ones via Mitsunobu reaction is reported. Using the highly reactive Mitsunobu coupling reagent combination *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide/tributylphosphine (TMAD–TBP) and a set of primary alcohols a small library of N1-alkylated dihydropyrimidones is obtained in good to excellent yields.

Key words: Mitsunobu reaction, selective alkylations, amides, dihydropyrimidones, Biginelli condensation

The multifunctionalized dihydropyrimidine scaffold **1** (DHPMs, 'Biginelli compounds') represents a heterocyclic system of remarkable pharmacological efficiency.[1] A wide range of biological activities has been ascribed to these partly reduced pyrimidine derivatives, and a number of lead compounds based on that structural core have been developed.[2,3] In general, DHPMs are available via Biginelli three-component condensation employing CH-acidic carbonyl compounds, aldehydes and urea building blocks.[1,4] This one-pot multicomponent reaction generally works best with urea itself, providing DHPM derivatives **1** in high yields. If N-monosubstituted alkyl ureas are employed under standard reaction conditions, lower yields are frequently obtained.[4–6] Furthermore, the commercial availability of substituted ureas is limited, thereby making the preparation of specific N1-substituted DHPMs often troublesome. In the context of a combinatorial program directed toward the synthesis of diverse DHPM libraries,[6] we required access to various, specifically substituted, N1-functionalized DHPM analogs. Since the selective N1-alkylation of DHPMs using standard alkylation conditions (i.e. alkyl halides in the presence of base) can be rather unselective and often leads to mixtures of N1/N3-, or dialkylated products,[7] we have considered the use of Mitsunobu conditions as an alternative to mediate the direct alkylation of DHPMs at the acidic N1-amide functionality with alcohols. Alcohols are usually stable and easy to handle, can be purchased with a broad variety of additional functional groups, and are therefore ideal building blocks for the preparation of compound libraries.

The Mitsunobu reaction is a versatile method for the conversion of aliphatic alcohols into alkylating agents in situ and under mild conditions.[8] Alkylations with the classical Mitsunobu set of reagents diethyl azodicarboxylate–triphenylphosphine (DEAD–TPP) are limited to rather acidic nucleophiles (N-, O- and C-acidic compounds) with a pK_a<11. For nucleophiles having a pK_a>11, more active Mitsunobu coupling reagents, like 1,1′-(azodicarbonyl)dipiperidine (ADDP) and *N*,*N*,*N*′,*N*′-tetramethylazodicarboxamide (TMAD), were developed by Tsunoda and co-workers.[9,10] In combination with tributylphosphine (TBP) these commercially available reagents can be used for the alkylation of low acidity nucleophiles such as amides.[11]

It appeared to us that the presence of the enamine moiety (O=C–C=C–NH) in the DHPM scaffold **1** would allow the regioselective alkylation of the N1-position under Mitsunobu conditions, taking advantage of the increased acidity of the hydrogen at N1 over N3. Here we report our results on the regioselective N1-monoalkylation of DHPMs utilizing Mitsunobu-type chemistry.

We started our investigations by exploring various classical Mitsunobu alkylation conditions employing DHPM **1** (R^1 = EtO, R^2 = Ph, R^3 = Me) as a model substrate and methanol as the alkylating agent (R^4 = Me). Disappointingly, all attempts to afford alkylation utilizing the traditional Mitsunobu diisopropyl azodicarboxylate (DIAD)–TPP tandem failed, despite numerous experimental variations in solvents (THF, dioxane, NMP, DMF), molar equivalents and sequence of addition of reagents, reaction time and temperature. Even after 24 hours reaction time, the conversion could not be increased to ca >20%.[12] Next, we tried to employ the ADDP–TBP combination (see above), which is known to mediate alkylations for systems with a pK_a>11.[9] Similar experimental variations as in the DIAD–TPP reagent tandem were performed, leading to some improvement in the overall alkylation process. The highest conversions **1** → **2** were achieved (75%) when 4.0 equivalents of each of the reagents (ADDP, TBP, MeOH) were used (THF, r.t., 4 h). However, this large excess of reagents caused problems in the subsequent work-up and purification. After considerable experimentation we discovered that TMAD is the Mitsunobu coupling reagent of choice for the selective N1-alkylation of DHPMs. In combination with TBP it is more reactive towards nucleophiles with a higher pK_a value, as reported by Tsunoda.[10] Optimization studies demonstrated that utilizing anhydrous dioxane as solvent showed a somewhat better performance than THF, and if methanol as alkylating reagent was used the optimum conditions employed

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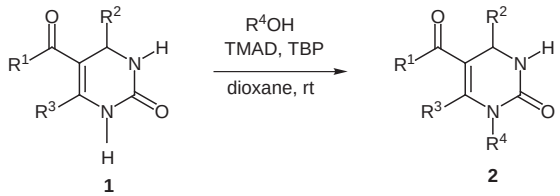
2.0 equivalents of MeOH, TMAD and TBP each. Under these set of conditions complete and selective conversion of **1** → **2** (Table 1, entry 1) was achieved within 1 hour at room temperature. On prolonged exposure (>2 h) to excess Mitsunobu reagents, slow formation of small amounts of the 1,3-dimethyl substituted DHPM was observed.[7] If other alcohols were used on the same DHPM substrate (Table 1, entries 2–5) somewhat different conditions had to be employed (2.5 equiv TMAD–TBP, 5.0 equiv R^4OH, 15 h, r.t.) in order to obtain complete conversions. In all cases, the Mitsunobu alkylation took place selectively at the N1-position.[13] Workup involved simple filtration from the reduced TMAD by-product, followed by direct purification of the filtrate by silica gel flash chromatography.[14]

Having optimized conditions for selective Mitsunobu N1-alkylations involving a variety of alcohols and one model DHPM substrate at hand (entries 1–5), we next applied this protocol to a small selection of 7 additional diverse DHPM derivatives obtained from a recent library synthesis.[6] Apart from methanol, other primary alcohols such as ethanol, propanol, hexanol, and benzylic type alcohols were successfully utilized providing the desired N1-alkylated DHPMs in moderate to good isolated yields (35–89%). Both electron withdrawing (entry 11) and donating substituents on the aromatic ring (entries 6–10, 12) were tolerated, and the alkylation procedure also worked well for C4-alkyl- (entries 13 and 14) and even C4-unsubstituted DHPM derivatives (entry 15). A variety of esters were accepted at the C5 position of the DHPM core, including methyl, ethyl, and benzyl esters. In addition, 5-acetyl analogs (entries 16 and 17) also provided the corresponding alkylated products in good yields. Note that longer alkyl chains in the C6 position (entry 12) were also tolerated.

Table 1 Mitsunobu Reaction (TMAD–TBP) of Functionalized DHPMs **1** with Alcohols R^4OH[a]



1 **2**

Entry	R^1	R^2	R^3	R^4	Yield (%)[b]
1	EtO	Ph	Me	Me	89
2	EtO	Ph	Me	Et	66
3	EtO	Ph	Me	*n*-Pr	42
4	EtO	Ph	Me	*n*-hexyl	35
5	EtO	Ph	Me	$PhCH_2$	61
6	MeO	3-Me-Ph	Me	Me	87
7	MeO	3-Me-Ph	Me	*n*-Pr	65
8	MeO	3-Me-Ph	Me	3-F-$PhCH_2$	45
9	EtO	3,4-$(MeO)_2$-Ph	Me	Me	80
10	EtO	3,4-$(MeO)_2$-Ph	Me	$PhCH_2$	54
11	EtO	3-NO_2-Ph	Me	Me	65
12	EtO	4-MeO-Ph	*n*-Pr	Me	74
13	EtO	Me	Me	Me	88
14	EtO	Me	Me	$PhCH_2$	59
15	$PhCH_2O$	H	Me	Me	76
16	Me	Ph	Me	Me	72
17	Me	Ph	Me	Et	55

[a] For R^4 = Me: 2.0 equiv MeOH, TMAD, and PBu_3; dioxane, 1 h, r.t. For other alcohols: 5.0 equiv R^4OH, 2.5 equiv TMAD and PBu_3; dioxane, 15 h, r.t. For details, see ref.[14]

[b] Isolated yield of pure product after silica gel flash chromatography. All compounds were characterized on the basis of their ^1H NMR and mass spectroscopic data.

We were however unsuccessful in coupling secondary alcohols such as 2-propanol to DHPMs under any type of reaction conditions. Even after 4 days of exposure to excess TMAD–TBP at room temperature or at elevated temperatures (60–100 °C in dioxane, THF or NMP) no conversion was observed. The use of the apparently more reactive cyanomethylenetributylphosphonium salts also proved to be ineffective.[15]

In conclusion, we have developed a simple procedure for the selective N1-alkylation of Biginelli dihydropyrimidines (DHPMs) via a Mitsunobu protocol involving the TMAD–TBP tandem as reagents. Therefore an additional point of diversity can now be rapidly introduced on the DHPM scaffold utilizing readily available primary alcohols as building blocks.

References

(1) Kappe, C. O. *Acc. Chem. Res.* **2000**, *33*, 879.

(2) See for example: (a) Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L. *Science* **1999**, *286*, 971. (b) Sidler, D. R.; Barta, N.; Li, W.; Hu, E.; Matty, L.; Ikemoto, N.; Campbell, J. S.; Chartrain, M.; Gbewonyo, K.; Boyd, R.; Corley, E. G.; Ball, R. G.; Larsen, R. D.; Reider, P. J. *Can. J. Chem.* **2002**, *80*, 646. (c) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254.

(3) For a recent review, see: Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043.

(4) (a) Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360. (b) Review: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937.

(5) Note that the successful use of *N*,*N*′-disubstituted and *N*-aryl-ureas in the Biginelli condensation is not well documented in the literature. In our own hands, these building blocks often produced mixtures of various unidentified products along with only small amounts of the desired dihydropyrimidones. See also: Kappe, C. O.; Stadler, A. *Org. Synth.* **2003**, *63*, in press.

(6) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624; and references cited therein.

(7) (a) Khanina, E. L.; Andaburskaya, M. B.; Duburs, G.; Zolotoyabko, R. M. *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.* **1978**, 197; *Chem. Abstr.* **1978**, *89*, 43319r. (b) Cho, H.; Takeuchi, Y.; Ueda, M.; Mizuno, A. *Tetrahedron Lett.* **1988**, *29*, 5405.

(8) For reviews on the Mitsunobu reaction, see: (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335. (c) Hughes, D. L. *Org. Prep. Proced. Int.* **1996**, *28*, 127.

(9) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639.

(10) Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Ito, S. *Chem. Lett.* **1994**, 539.

(11) In general, examples found in the literature are limited to relatively acidic sulfonamides or trifluoroacetamides. For some recent examples involving amides, see: (a) Kozai, S.; Takaoka, S.; Maruyama, T. *Tetrahedron Lett.* **2002**, *43*, 2633. (b) Evans, P. A.; Manangan, T. *Tetrahedron Lett.* **2001**, *42*, 6637. (c) Bombrun, A.; Casi, G. *Tetrahedron Lett.* **2002**, *43*, 2187. (d) Reichwein, J. F.; Liskamp, R. M. J. *Tetrahedron Lett.* **1998**, *39*, 1243.

(12) Note that the use of high-temperature microwave chemistry was unsuccessful here. For microwave-assisted Mitsunobu alkylations, see: Steinreiber, A.; Stadler, A.; Mayer, S. F.; Faber, K.; Kappe, C. O. *Tetrahedron Lett.* **2001**, *42*, 6283.

(13) ^{1}H NMR spectroscopy (characteristic 3–5 Hz coupling between C4-H and N3-H) readily allows one to distinguish between N1-, N3- and O-alklyated DHPMs. For details and the selective preparation of N3-alkylated DHPMs, see: Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.* **1989**, *26*, 55.

(14) **Typical Experimental Procedure (Outlined for Entry 5):** In a dry 5 mL reaction vial the appropriate DHPM (R^1 = EtO, R^2 = Ph, R^3 = Me; 26 mg, 0.10 mmol) was dissolved in anhyd dioxane (0.5 mL) at 70 °C. After cooling to r.t. benzyl alcohol (54 mg, 0.50 mmol, 52 μL), TBP (51 mg, 0.25 mmol, 62 μL) and TMAD (43 mg, 0.25 mmol) were added. The vial was sealed, flushed with argon and the reaction mixture shaken for 15 h at r.t. The white precipitate that was formed was filtered off, and the crude reaction mixture separated by silica gel flash chromatography (DCM:EtOAc 1:1) providing 21.2 mg (61%) of N1-alkylated DHPM as colorless crystals, mp 155 °C (lit.[6] 155–156 °C). ^{1}H NMR (DMSO-d_6): δ = 1.09 (t, *J* = 7.1 Hz, 3 H), 2.36 (s, 3 H), 4.02 (q, *J* = 7.1 Hz, 2 H), 4.84 and 5.09 (2 d, *J* = 16.6 Hz, 2 H), 5.24 (d, *J* = 3.2 Hz, 1 H), 7.06 (d, *J* = 7.0 Hz, 2 H), 7.22–7.35 (m, 8 H), 8.16 (d, *J* = 3.3 Hz, 1 H). MS (APCI): *m/z* (%) = 351(28) [M^+].

(15) (a) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518. (b) Tsunoda, T.; Ozaki, F.; Ito, S. *Tetrahedron Lett.* **1994**, *35*, 5081. (c) Tsunoda, T.; Nagino, C.; Oguri, M.; Ito, S. *Tetrahedron Lett.* **1996**, *37*, 2459.