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New Entry to a Three-Component Pyrimidine Synthesis by TMS–Ynones via Sonogashira Coupling

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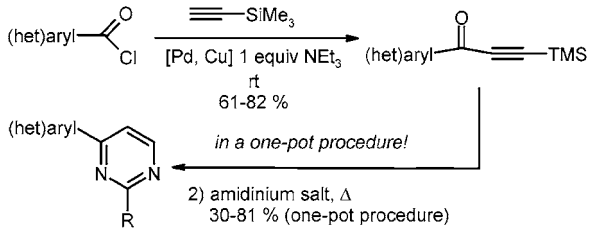
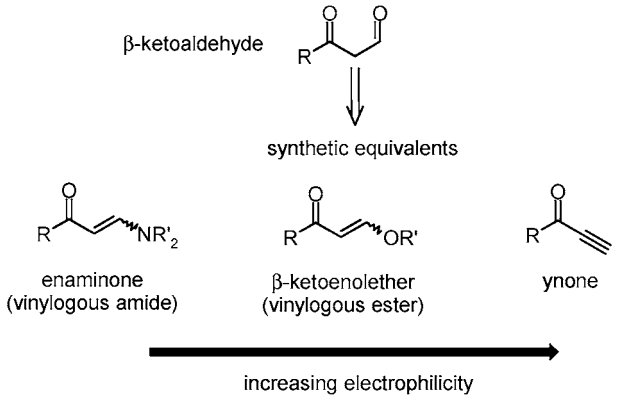
ABSTRACT



TMS–ynones are versatile synthetic equivalents of β-keto aldehydes and can be readily synthesized in an atom-economical fashion by coupling (het)aroyl chlorides and (TMS)–acetylene with only one equiv (!) of triethylamine under Sonogashira conditions. This mild ynone synthesis is also a suitable entry to 2,4-disubstituted pyrimidines in the sense of a one-pot three-component reaction, i.e., a coupling–addition–cyclocondensation sequence.

1,3-Dicarbonyl compounds such as β-keto aldehydes[1] are very important and well-established three-carbon building blocks for cyclocondensations in heterocyclic chemistry.[2] However, synthetic equivalents (Scheme 1) of β-keto aldehydes such as β-ketoacetals,[3] vinylogous esters (β-ketoenolethers),[4] or vinylogous amides (enaminones)[5] are often easier to handle and provide a broader scope of regiocontrol in cyclocondensations. Besides their enormous synthetic potential, enaminones[5] in their own right, β-keto aldehydes are highly pharmacologically active and possess pronounced anticonvulsant[6] and nonsteroidal antiinflammatory activities.[7] Interestingly, a common synthetic pathway to β-ketoacetals, β-ketoenolethers, and enaminones is the Michael addition of alcohols or amines to alkynones (ketovinylation)[8] that are even more electrophilic than all other synthetic equivalents of β-keto aldehydes (Scheme 1).

Scheme 1. Synthetic Equivalents of β-Keto Aldehydes



(1) For a very recent review on reactions of acetylacetaldehyde, see e.g.: Quintanilla-Licea, R.; Teuber, H.-J. *Heterocycles* **2001**, *55*, 1365.

(2) (a) Eicher, T.; Hauptmann, S. *Chemie der Heterocyclen*; Georg Thieme Verlag: Stuttgart, 1994. (b) Gilchrist, T. L. *Heterocyclic Chemistry*; Longman Scientific and Technical: Essex, 1992.

(3) (a) Takazawa, O.; Mukaiyama, T. *Chem. Lett.* **1982**, 1307. (b) Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15.

(4) (a) Clerici, A.; Pastori, N.; Porta, O. *Tetrahedron* **2001**, *57*, 217. (b) Effenberger, F.; Maier, R.; Schoenwaelder, K. H.; Ziegler, T. *Chem. Ber.* **1982**, *115*, 2766.

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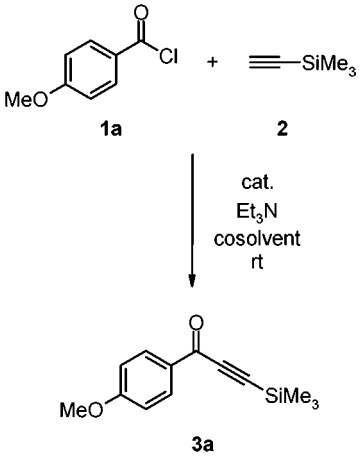
A limitation of this approach, however, is the inherent high reactivity of terminal ethynyl ketones toward nucleophiles. On the other hand, (trimethylsilyl)ethynyl ketones are significantly more stable than the parent ynones and can be prepared either (a) by the addition of lithium (trimethylsilyl)-acetylide to Weinreb amides,[9] (b) by Friedel−Crafts acylation of bis(trimethylsilyl) acetylene,[10] or (c) by Stille coupling of acid chlorides with (TMS)−ethynyl tributylstannane.[11] However, the most elegant and atom-economical way of transforming the acid chlorides, i.e., the ultimate starting compounds, into (TMS)−ethynyl ketones is the cross-coupling of (TMS)−acetylene under the conditions of the Sonogashira coupling. Although the Sonogashira coupling of acid chlorides and terminal alkyl or (hetero)aryl alkynes proceeds smoothly,[12] to our knowledge, the successful coupling of acid chlorides and (TMS)−acetylene has not been reported so far and in attempted experiments only led to the formation of bis(TMS)−butadiyne.[13] As part of our program directed to design novel multicomponent reactions based on in situ activation of alkynes by Sonogashira coupling,[14] we have now focused on coupling−amination sequences. Here, we wish to communicate the formation of (TMS)−ethynyl ketones under altered Sonogashira conditions and the first three-component syntheses of enaminones and 2,4-substituted pyrimidines.

First, we wanted to scout the conditions for the hitherto unknown coupling between benzoyl chlorides and (TMS)−acetylene and we chose as model reaction partners *p*-methoxybenzoyl chloride (**1a**) and (TMS)−acetylene (**2**) at room temperature with various catalyst combinations and amounts of triethylamine as a base (Scheme 2).

Scheme 2. Coupling of *p*-Methoxybenzoyl Chloride (**1a**) and (TMS)−Acetylene (**2**)



Neither the classical conditions (entry 1)[12] nor the copper-catalyzed variation (entry 2),[15] where triethylamine is applied as a solvent, gave rise to the isolation of the (TMS)−alkynone **3**.[16] However, reducing the amount of triethylamine to stoichiometric equivalents allowed the isolation of ynone **3** in good yield. Surprisingly, the reaction proceeds so quickly that both starting materials are completely consumed after 1 h (entry 4) and prolonging the reaction time with only a slight excess of triethylamine causes a significant decrease in the yield (entry 3). Therefore, the key to the successful preparation of (TMS)−alkynones **3** is *the addition of only 1 equiv of triethylamine* as the HCl-scavenging base. In accordance with Sonogashira couplings, the absence of the copper cocatalyst causes the reaction time to be prolonged considerably (entry 5).

Applying these peculiar conditions to a variety of (hetero)-aroyl chlorides **1**, the corresponding (TMS)−alkynones **3** are

Table 1. Conditions for the Coupling of *p*-Methoxybenzoyl Chloride (**1a**) and (TMS)−Acetylene (**2**)[a]

entry	catalyst[a]	amount of Et_3N	cosolvent	time (h)[b]	yield of **3a** (%)[c]
1	Pd/Cu	as a solvent	none	1	0
2	Cu	as a solvent	none	24	0
3	Pd/Cu	1.25 equiv	THF	48	22
4	Pd/Cu	1 equiv	THF	1	82
5	Pd	1 equiv	THF	48	79

[a] Reaction conditions: 1.0 equiv of *p*-methoxybenzoyl chloride (**1a**) and 1.0 equiv of (TMS)−acetylene (**2**), 0.02 equiv of $(Ph_3P)_2PdCl_2$, and/or 0.04 equiv of CuI, various amounts of NEt_3, and THF (5 mL/mmol acid chloride). [b] Consumption of (TMS)−acetylene was monitored by TLC, and the reaction was stopped after complete conversion. [c] Yields refer to isolated yields of compound **3** after chromatography estimated to be ≥95% pure as determined by NMR spectroscopy.

(5) For reviews on the synthetic potential of enaminones in heterocycle syntheses, see e.g.: (a) Smirnova, Y. V.; Krasnaya, Z. A. *Russ. Chem. Rev.* **2000**, *69*, 1021. (b) Michael, J. P.; De Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979. (c) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1997**, *67*, 207. (d) Cimarelli, C.; Palmieri, G. *Recent Res. Devel. Org. Chem.* **1997**, *1*, 179. (e) Michael, J. P.; Gravestock, D. *Pure Appl. Chem.* **1997**, *69*, 583. (f) Kuckländer, U. Chemistry of Enamines. In *The Chemistry of Functional Groups*; S. Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1994; p 523. (g) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277.

(6) (a) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Butcher, R. J.; Edafiogho, I. O.; Stables, J. P.; Cooke, N.; Goodwin, A. M.; Smith, C. A.; Scott, K. R. Eur. *J. Med. Chem.* **2002**, *37*, 635. (b) Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Stables, J. P.; Powell, C. B.; Scott, K. R. *Curr. Med. Chem.* **2000**, *7*, 417. (c) Scott, K. R.; Rankin, G. O.; Stables, J. P.; Alexander, M. S.; Edafiogho, I. O.; Farrar, V. A.; Kolen, K. R.; Moore, J. A.; Sims, L. D.; Tonnut, A. D. *J. Med. Chem.* **1995**, *38*, 4033. (d) Edafiogho, I. O.; Alexander, M. S.; Moore, J. A.; Farrar, V. A.; Scott, K. R. *Curr. Med. Chem.* **1994**, *1*, 159.

(7) Dannhardt, G.; Bauer, A.; Nowe, U. *Arch. Pharm. (Weinheim, Ger.)* **1997**, *330*, 74.

(8) (a) Bromidge, S. M.; Entwistle, D. A.; Goldstein, J.; Orlek, B. S. *Synth. Commun.* **1993**, *23*, 487. (b) Tripathi, V. K.; Venkataramani, P. S.; Mehta, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 36. (c) Venkataramani, P. S.; Saxena, N. K.; Tripathi, V. K.; Mehta, G. *Indian J. Chem.* **1975**, *13*, 852. (d) Gais, H. J.; Hafner, K.; Neuenschwander, M. *Helv. Chim. Acta* **1969**, *52*, 2641.

(9) Bromidge, S. M.; Entwistle, D. A.; Goldstein, J.; Orlek, B. S. *Synth. Commun.* **1993**, *23*, 487.

(10) (a) Newman, H. *J. Org. Chem.* **1973**, *38*, 2254. (b) Walton, D. R. M.; Waugh, F. *J. Organomet. Chem.* **1972**, *37*, 45. (c) Birkofer, L.; Ritter, A.; Uhlenbrauck, H. *Chem. Ber.* **1963**, *96*, 3280.

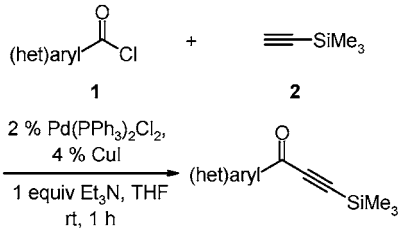
(11) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549.

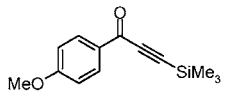
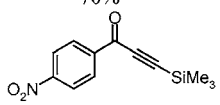
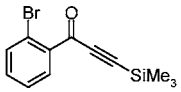
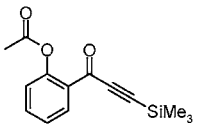
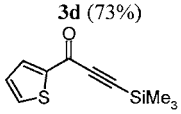
(12) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777.

(13) Sashida, H. *Synthesis* **1998**, 745.

(14) (a) Karpov, A. S.; Rominger, F.; Müller, T. J. J. *J. Org. Chem.* **2003**, *68*, 1503. (b) Yehia, N. A. M.; Polborn, K.; Müller, T. J. J. *Tetrahedron Lett.* **2002**, *43*, 6907. (c) Braun, R. U.; Zeitler, K.; Müller, T. J. J. *Org. Lett.* **2001**, *3*, 3297. (d) Müller, T. J. J.; Robert, J. P.; Schmälzlin, E.; Bräuchle, C.; Meerholz, K. *Org. Lett.* **2000**, *2*, 2419. (e) Müller, T. J. J.; Ansorge, M.; Aktah, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 1253.

Table 2. Synthesis of (Trimethylsilyl)−Ethynyl Ketones **3** by Sonogashira Coupling of Acid Chlorides **1** and (TMS)−Acetylene (**2**)[a]



entry	acid chloride RCOCl **1**	(TMS)-alkynone **3** (Yield %)[b]
1	R = *p*-methoxyphenyl (**1a**)	 **3a** (82%), Stille coupling: 70%[18,c]
2	R = *p*-nitrophenyl (**1b**)	 **3b** (65%), Stille coupling: 51%[11]
3	R = *o*-bromophenyl (**1c**)	 **3c** (61%), Stille coupling: 45%[13]
4	R = *o*-acetyl hydroxyphenyl (**1d**)	 **3d** (73%)
5	R = 2-thienyl (**1e**)	 **3e** (82%)

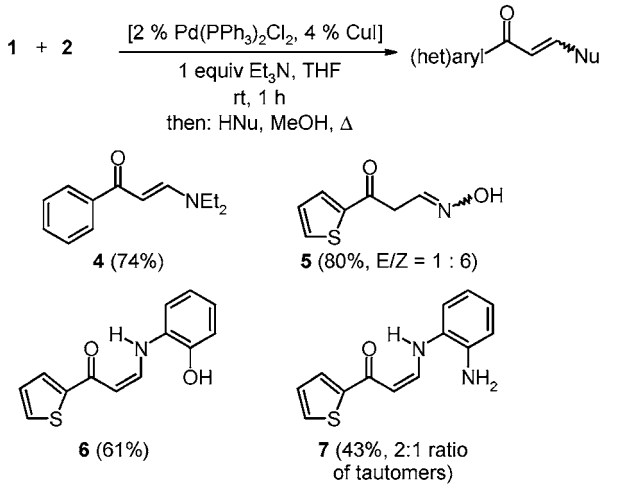
[a] Reaction conditions: 1.0 equiv of (hetero)aroyl chloride **1** and 1.0 equiv of (TMS)−acetylene (**2**), 1.0 equiv of triethylamine, 0.02 equiv of $(Ph_3P)_2PdCl_2$ and/or 0.04 equiv of CuI in THF (5 mL/mmol acid chloride). [b] Yields refer to isolated yields of compounds **3** after chromatography estimated to be ≥95% pure as determined by NMR spectroscopy. [c] After desilylation.

obtained in moderate to good yield (Table 2).[17] It is noteworthy that the yields of this modified Sonogashira coupling are considerably higher than those of comparable Stille couplings (entries 1−3). In contrast to the Weinreb approach, sensitive or fragile functionalities such as nitro, bromo, or acetoxy substituents are tolerated.

The structure of the (TMS)−alkynones is unambiguously supported by the appearance of the characteristic singlets for the TMS−methyl proton resonances between δ 0.1 and 0.3 in the ^{1}H NMR spectra. In the ^{13}C NMR spectra, these carbon resonances appear between δ −1.0 and −0.7, the signals of the quaternary carbon nuclei of the triple bonds appear between δ 99−104, and those of the carbonyl groups lie between δ 169 and 175.

With this convenient catalytic access to (TMS)−ynones **3** in hand and reconsidering the mild reaction conditions, we next tested the transformation of **3** into β-keto aldehyde synthetic equivalents by the consecutive addition of a nucleophile in the sense of a coupling−addition sequence (Scheme 3).

Scheme 3. Coupling−Addition Sequence to β-Keto Aldehyde Synthetic Equivalents



After the complete conversion of the acid chloride **1**, equimolar amounts of nitrogen nucleophiles (HNu) such as diethylamine, hydroxylamine hydrochloride/ sodium carbonate, *o*-amino phenol, or *o*-phenylene diamine were added in a small amount of methanol to the reaction mixture to furnish, after boiling for short periods of time, the enaminones **4**, **6**, and **7** or the β-ketoxime **5** in moderate to good yields.[19]

Expectedly,[8a] these nucleophilic additions proceed with the concomitant loss of the trimethylsilyl group. Interestingly,

(15) (a) Chowdhury, C.; Kundu, N. G. *Tetrahedron Lett.* **1996**, *37*, 7323. (b) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011.

(16) Unfortunately, we could not reproduce the copper-catalyzed reaction of *p*-methylbenzoyl chloride with (TMS)−acetylene in dry triethylamine under nitrogen at room temperature as claimed in ref 15.

(17) **Typical Procedure** (**3d**, Table 2, entry 4). A stirred mixture of 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$ and 7 mg (0.04 mmol) of CuI in 5 mL of THF was stirred and degassed with nitrogen before 0.14 mL (1.00 mmol) of triethylamine, 199 mg (1.00 mmol) of acid chloride **1d**, and 0.14 mL (1.00 mmol) of trimethylsilyl acetylene were added successively. The reaction mixture was then stirred for 1 h at room temperature until the complete consumption of alkyne (monitored by TLC). The solvents were evaporated, and the residue was chromatographed on silica gel (diethyl ether/ pentane 1:9) to give 190 mg (73%) of analytically pure **3d** as a yellow oil. ^{1}H NMR ($CDCl_3$, 250 MHz): δ 0.30 (s, 9 H), 2.36 (s, 3 H), 7.11 (d, J = 7.9 Hz, 1 H), 7.38 (t, J = 7.9 Hz, 1 H), 7.60 (t, J = 7.9 Hz, 1 H), 8.22 (d, J = 7.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ −0.9 (CH_3), 20.8 (CH_3), 99.9 ($C_{quat.}$), 101.2 (C_{quat}), 123.9 (CH), 126.0 (CH), 128.7 (C_{quat}), 133.4 (CH), 135.7 (CH), 150.0 (C_{quat}), 169.2 (C_{quat}), 175.4 (C_{quat}). EI +Q1MS (*m*/*z* (%)): 260 (M^+, 2), 245 ($M^+ - CH_3$, 42), 217 ($M^+ - CH_3CO$, 37), 203 ($M^+ - CH_3 - CH_2CO$, 100), 73 (Me_3Si^+, 9). IR (neat): $\tilde{\nu}$ 2962 cm^{-1}, 2902, 2153, 2095, 1772, 1646, 1604, 1481, 1368, 1239, 1019, 849, 764. HRMS calcd for $C_{14}H_{16}O_3Si$, 260.0864; found, 260.0881.

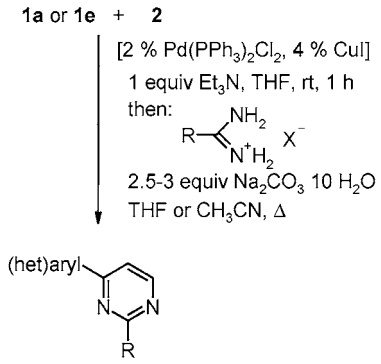
(18) Miller, R. D.; Reiser, O. *J. Heterocycl. Chem.* **1993**, *30*, 755.

(19) Structures **4**−**7** were unambiguously assigned by ^{1}H, ^{13}C, and NOESY NMR. These assignments are additionally supported by IR and MS spectra, as well as correct elemental analyses.

under the chosen mild reaction conditions, no cyclocondensations occurred with the applied bidentate nucleophiles.

However, upon addition of amidinium or guanidinium salts together with 2.5−3 equiv of sodium carbonate decahydrate to the (TMS)−ynones **3** in a one-pot process, the pyrimidines **8** were obtained in modest to good yields (Scheme 4).[20] The

Scheme 4. Coupling−Addition Synthesis of 2,4-Disubstituted Pyrimidines



8a (het)aryl = 2-thienyl, R = NH_2 (51%)
8b (het)aryl = *p*-anisyl, R = NH_2 (49%)
8c (het)aryl = 2-thienyl, R = *p*-nitrophenyl (30%)
8d (het)aryl = 2-thienyl, R = *p*-anisyl (81%)

formation of the pyrimidyl core is strongly supported by the appearance of the characteristic AB-spin patterns in the ^{1}H NMR spectra at δ 7.07−7.28 (C^5H) and δ 8.25−8.83 (C^6H) with coupling constants of 5.2−5.4 Hz.

In conclusion, we have developed a straightforward catalytic access to (TMS)−ynones, synthetic equivalents of β-keto aldehydes. The crucial point for the successful Sonogashira coupling of (hetero)aroyl chlorides and (TMS)−acetylene is the application of only 1 equiv of triethylamine as the necessary base. In addition, this new protocol represents a more atom-economical alternative to the state of the art Stille synthesis of (TMS)−ynones. The extremely mild reaction conditions (stoichiometric amount of triethylamine at room temperature) are particularly well suited for the development of novel multicomponent reactions. Thus, we have disclosed a new one-pot, three-component synthesis of 2,4-substituted pyrimidines, a pharmaceutically important class of pyrimidines.[21] Studies addressing this novel concept of catalytic in situ activation of alkynes as an entry to multicomponent reactions and the extension of this new pyrimidine synthesis to pharmaceutically and, from a materials science point of view, highly interesting targets are currently underway.

Acknowledgment. The financial support of the Fonds der Chemischen Industrie and the Dr.-Otto-Röhm Gedächtnisstiftung is gratefully acknowledged. We also cordially thank Andrea Seehuber for experimental assistance.

Supporting Information Available: Experimental procedures and characterization of compounds **3**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035212Q

(20) **Typical Procedure** (**8d**): A stirred mixture of 14 mg (0.02 mmol) of $Pd(PPh_3)_2Cl_2$ and 7 mg (0.04 mmol) of CuI in 5 mL of THF was stirred and degassed with nitrogen before 0.14 mL (1.00 mmol) of triethylamine, 147 mg (1.00 mmol) of acid chloride **1e**, and 0.14 mL (1.00 mmol) of trimethylsilyl acetylene were added successively. The reaction mixture was then stirred for 1 h at room temperature until the complete consumption of alkyne (monitored by TLC). Then, 973 mg (3.40 mmol) of $Na_2CO_3 \cdot 10\ H_2O$, 224 mg (1.20 mmol) of *p*-methoxy benzamidine hydrochloride, and 5 mL of methanol were added, and the reaction mixture was heated to reflux temperature for 12 h. The solvents were evaporated, and the residue was chromatographed on silica gel (ethyl acetate/hexanes 1:4) to give 217 mg (81%) of analytically pure **8d** as white crystals, mp 82 °C (methanol). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.80 (s, 3 H), 6.93 (d, J = 9.1 Hz, 2 H), 7.08 (dd, J = 5.1, 3.8 Hz, 1 H), 7.28 (d, J = 5.3 Hz, 1 H), 7.45 (dd, J = 5.1, 1.2 Hz, 1 H), 7.71 (dd, J = 3.8, 1.2 Hz, 1 H), 8.41 (d, J = 9.1 Hz, 2 H), 8.62 (d, J = 5.3 Hz, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 55.3 (CH_3), 112.0 (CH), 113.9 (CH), 127.4 (CH), 128.3 (CH), 129.9 (CH), 130.1 (CH), 143.0 (C_{quat}), 156.3 (C_{quat}), 157.1 (CH), 159.0 (C_{quat}), 162.0 (C_{quat}), 164.1 (C_{quat}). FAB$^+$ MS *m*/*z* (%): 269 (M^+, 100). IR (KBr): $\tilde{\nu}$ 1562, 1416, 1252 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2OS$ (268.3): C, 67.14; H, 4.51; N, 10.44. Found: C, 66.78; H, 4.51; N, 10.29.

(21) For the significance of 2,4-disubstituted pyrimidines as tyrosine kinase inhibitors see, e.g.: (a) Traxler, P.; Bold, G.; Buchdunger, E.; Caravatti, G.; Furet, P.; Manley, P.; O'Reilly, T.; Wood, J.; Zimmermann, J. *Med. Res. Rev.* **2001**, **21**, 499. (b) Zimmermann, J.; Buchdunger, E.; Mett, H.; Meyer, T.; Lydon, N. B. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 187.